THE HYPOTHALAMUS AND SLEEP REGULATION

An Experimental and Morphological Study

By

STIG RANSTRÖM

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MED. LIC., VÄSTMANL.-DALA

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From the Pathological Institution at the University
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PREFACE.

The main part of the present work has been performed at the Pathological Institution in Upsala. To Professor Robin Fåhræus, the head of the institution, and to Prosector Nils Gellerstedt I am greatly indebted for all the kind interest, stimulating and valuable discussions, and important criticism with which they have supported my investigations.

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Upsala, April 1947. *S. R.*

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INTRODUCTION.

The literature concerning the sleep function is comprehensive. Owing to the fact that the many sleep theories propounded during the course of time have been so very diverse, the history of the sleep problem has become an enticing subject for monographic surveys. The earliest of these seems to be Iossio's *Tractatus novus de voluptate et dolore, risu et fletu, somno et vigilia* published in the year 1603, and from this work the majority of later authors have apparently derived their knowledge as to the different views held in older times. In modern times two large monographs are specially noteworthy. They complete each other in such a manner that the earlier of them, Piéron's *Le problème physiologique du sommeil* of 1912, deals with the literature up to this year, while the latter, Kleitman's *Sleep and wakefulness,* published in 1939, is largely restricted to the literature between 1912 and 1939 under reference to Piéron's work. Some comprehension of the extensiveness of the literature is obtained from the number of references in the two large monographs. These are listed in Piéron's work of 1399 and in Kleitman's issued 1434. As Kleitman's work was published so relatively recently there seems little reason for occupying space here with an exhaustive historic survey of the sleep problem. Therefore only a quite brief account will be rendered of the more important experiences and theories within this field of research. Readers who desire a wider historic view of the development of the sleep problem are therefore referred to the above mentioned monographs, and especially to that of Kleitman which gives a detailed account of the research of the most recent decades and most valuable results.

Other more or less exhaustive monographs have been published by Nachmansohn 1927, Sarason (ed.) 1929, Zweig 1930, Engebretsen 1934, Müller 1940 and Harrison 1940.

CHAPTER I.

The chief outlines of the development of the sleep problem.

1. Earlier neural and humoral theories of sleep.

Few physiological phenomena have more often been the object of theoretic speculations than sleep. The alternation common both to the human and the animal between the active state of wakefulness and the inactive condition of being asleep has seemed for ages to be obscure. Already early however it was clear that the alternation between wakefulness and sleep appeared to be due to some mechanism within the organism and that only secondarily is it influenced by other factors of the world around such as light and darkness. It was accordingly natural that the early authors assumed the existence of an endogenous power inducing the alternation between wakefulness and sleep. In other words the basis of the assumption was that there must be a regulative mechanism for sleep within the organism.

In respect of the human being, sleep is generally monophasic in the sense that twenty-four hours include one period of wakefulness and one period of sleep. On the other hand, during the first year of life the sleep-wakefulness rhythm is polyphasic, by which means, that several periods of alternating sleep and wakefulness succeed each other during the twenty-four hours. At the termination of the first, and during the second year, the type of the curve gradually becomes monophasic, in that the night sleep increases in duration at the expense of the day sleep periods which become fewer and shorter. Among some animals, such as the monkey, dog and cat, the sleep-wakefulness cycle is likewise monophasic. Other animals, for instance rodents, manifest a marked polyphasic twenty-four hour

rhythm with as many as some twenty periods of sleep or sleep-like states.

Since consciousness is lost during sleep, the brain, in its entirety, came early to play an important rôle in the discussion concerning the regulation mechanism of sleep.

In the 17th and 18th centuries there were animated discussions as to whether the cause of sleep was anemia or hyperemia of the brain. Modern investigations (e. g. Gibbs *et al.* 1935) have elucidated the fact however that, in respect of sleep, there is no characteristic change of the amount of blood circulating in the brain, but that the blood content of the brain changes from time to time even during sleep.

It was not until the elucidation of the histology and functional behaviour of the central nervous system began, during the latter half of the 19th century, that firmer grounds for the conception of sleep function were created. Brown-Sequard (1889) assumed that a reflex action of the inhibitory type resulted in sleep, and this idea reached its most prominent form in Pavlov's (1923) theory of sleep as a conditioned reflex. To some extent the hypothesis of Claparède (1904) is related to these views. He maintains that sleep can be conceived as being an instinct reflex serving to prevent exhaustion of the organism. If these and even other closely related theories may possibly be correct, in themselves, they afford however no actual explanation of the physiological behaviour which results in sleep. A theory of quite another character than those already mentioned is that of Cajal (1895) and others, which implies that sleep is due to dendritic retraction (ameboid movement in neurons or neuroglia cells). This theory however lacks proof and is now conclusively set aside as improbable (cf Müller 1940).

The development of medical chemistry at the close of the 19th and during the 20th century likewise influenced the discussions on the sleep regulation. A number of substances both chemically defined and hypothetical have been presumed to affect the functions of the central nervous system in such a manner that sleep ensues. Of the former type of substances can be mentioned, lactic acid (Preyer 1875) and carbonic acid (Dubois 1896) intoxication, accumulation of cholesterol (Brissemoret & Joanin 1911) and of calcium (Cloetta 1936) in the brain. Later research has been able to verify some of the observations which are basic for the theories concerned, but

according to modern opinion these rhythmic changes in the concentrations of the substances in question should be regarded as the results of or coincidental phenomena to sleep more than as causes of the same.

As an instance of the nondefined chemical substances PIÉRON's hypnotoxins might be selected. PIÉRON's basic idea was that during the state of wakefulness, substances might be formed within the organism as a whole, due to gradual metabolic overwork. On attaining a sufficiently high concentration these would induce exhaustion and sleep through the poison-effect on the central nervous system. With a view to experimentally testing the accurancy of this assumption, PIÉRON injected cerebrospinal fluid of dogs which had been kept awake several days, into the fourth ventricle of thoroughly rested, wide-awake dogs. These latter manifested listlessness and somnolence. PIÉRON called the substances responsible for this effect hypnotoxins. IVY & SCHNEEDORFF (1937) verified PIÉRON's results later, but afterwards expressed themselves with a certain amount of reservation because the injection regularly involved a considerable rise of temperature, and partly because, in some cases, even fluid from thoroughly rested animals brought those injected into a state of somnolence.

It is a fact, as KLEITMAN has pointed out, that a number of arguments can be raised in opposition to all these theories which are based on the formation of various kinds of exhaustion toxin as the primary factor in the regulation of sleep. One of the strongest of these objections seems to be that the human sense of tiredness and inclination to sleep, does not gradually increase in the case of prolonged abstinence from sleep, but in reality that rhythm is displayed which, widely seen, coincides with the physiological sleep-wakefulness cycle.

FORSGREN (1930) and HOLMGREN (1931) feel that they have grounds for their assumption that the liver of rabbits and white mice during certain phase of the day contains substances which can induce sleep when injected in experimental animals of the same kind. If this is right, the substances in question could scarcely have anything to do with the physiological regulation of sleep, one reason being that the rhythm of the liver is monophasic with regard to the twenty-four hours, while the sleep-wakefulness curve among the experimental animals in question is decidedly polyphasic.

The endocrine organs have also been drawn into the discussion on the regulation of sleep. It is obvious that these organs can be of importance to the sleep function, to that extent that the dysfunctions within the endocrine organs are sometimes combined with disturbances of sleep. Hypersomnia in underfunction and hyposomnia in overfunction of the thyroid gland are common symptoms long since known in myxedema and toxic goitre. That was the reason why the thyroid gland was the first endocrine organ which was drawn into the discussion on the cause of sleep.

The hypophysis was however the endocrine gland that came to be spoken of later in connection with the sleep function. Hypophysial disturbances involving disturbances in the sleep-wakefulness cycle are not unusual. Hypophysial extracts injected into the cerebral ventricular system of test animals have been known to induce sleep (Salmon 1929). There have also been favourable effects of the same extracts in cases of sleep disturbances connected with deranged hypophysial function (Beyermann 1930, McGovern 1932). Salmon (1929, 1942) maintains in several of his works that a hormone is formed in the posterior lobe of the hypophysis, which produces vasoconstriction within the diencephalon and that the subsequent underfunction of these centres would induce sleep. On the other hand, according to Salmon, the anterior lobe should have a contrary function in the regulation of sleep because this part of the hypophysis forms a hormone, an »antitoxic» substance, designed to guarantee undisturbed function of the diencephalon. This in its turn would consequently be a condition for the maintainance of the state of wakefulness.

Zondek & Bier (1932) are of the opinion that the bromine content of the hypophysis is reduced during sleep while that of the hypothalamus increases. These authors also isolated a substance containing bromine from hypophysial tissue, which substance they called »sleep hormone». Later authors (Holz & Roggenbau 1933, Neufeld 1936) however have not been able to verify these results.

The rôle of the above mentioned endocrine glands, as primary organs in the regulation of sleep, is argued against most definitely by the circumstance that the typical diurnal rhythm of sleep as regards both the human being and the animal is maintained on the whole even if the organs in question are exstirpated or put out of function by pathological processes (cf Kleitman).

2. The centre for sleep regulation and its localization.

When the central nervous system became ever increasingly mapped out in such a manner that every function could be projected on certain determined parts of the brain or spinal cord, it was found expedient to investigate the part or parts of the brain which might be of special importance with regard to sleep regulation. During the sleep research of recent decades, interest has been more and more drawn towards the vegetative centres of the brain stem, that is to say, the grey substance in connection with the third ventricle and the Sylvian aqueduct. As so often is the case in the history of medicine it was the patho-anatomy that gave the fixed starting-point in these respects. The patho-anatomical study of cases in which sleep disturbances formed part of the syndrome, has thus been an important method in the attempt to find out the location of the sleep regulation.

a. Encephalitis lethargica.

The first to avail himself of this method appears to have been MAUTHNER who, in 1890, described cases of an epidemic disease with a deadly course, which went under the name of »nona». The chief clinical symptoms of this disease, which was a form of encephalitis, included somnolence, general muscular weakness and oculo-motor symptoms. MAUTHNER connected the sleep disturbances with the patho-anatomical changes within the grey matter adjacent to the lower part of the third ventricle as well as the anterior part of the aqueduct (»das zentrale Höhlengrau»), but his publications give no further informations as to the exact extent and type of the changes.

The greatest credit for the elucidation of the patho-anatomical changes which form the basis of sleep disturbances in encephalitis is due to VON ECONOMO (1923) who through his basic research on epidemic encephalitis, created the first real points of departure for discussing the localization of the sleep function within the nervous system. The form of disease which he described, received, as is known, the name *encephalitis lethargica.* The clinical syndrome in the acute stage of the variant in which sleep disturbances occur the most frequently, the ophtalmoplegic-somnolent type, coincides on the whole with the one MAUTHNER described earlier. (There are also other variants of the disease with other main symptoms, especially

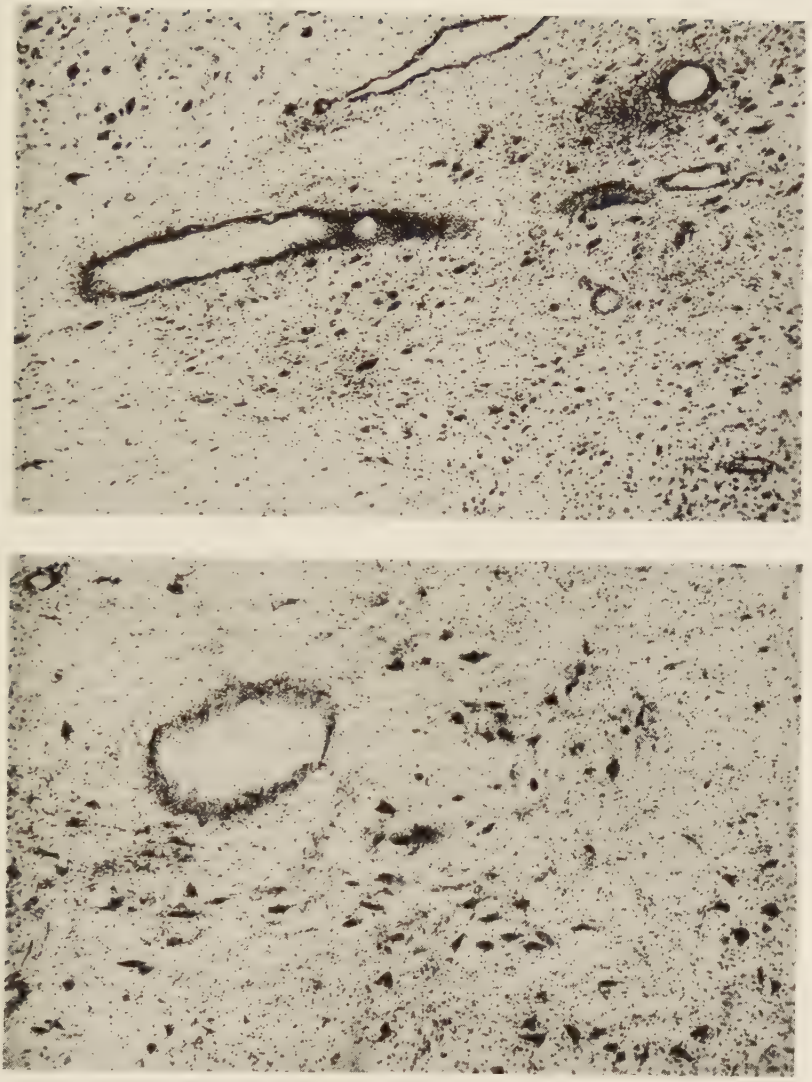

Fig. 1 (microphotographs, Nissl stain). The juxtaventricular region from two cases of acute fatal encephalitis lethargica showing perivascular round cell infiltration as histologic main-symptom. The nerve cells and the tissue structure are well preserved.

those derived from the extrapyramidal system, but these are of minor interest in this connection.) Psychic symptoms and state of anxiety often occur as a prodromal stage. The stage of somnolence can be of exeedingly variable duration (from days to months). It may set in either gradually or acutely, and it may subside gradually or suddenly. The disturbance in the consciousness can be of varying degree from light somnolence to coma. In the chronic stage of the disease which as a rule manifests itself clinically long time after the acute stage, and which frequently gives the picture of Parkinsonism, hyposomnia appears as a common symptom. It may be of varying severity from case to case, and is usually very little affected by the available drugs, at least of ordinary dosage.

The patho-anatomical changes in the acute stage which are thus more fully elucidated by VON ECONOMO, consist in an encephalitic process within the juxta-ventricular parts of the brain stem and also within somewhat further laterally situated cerebral parts, the pallidum and, though to a lesser extent, the neostriatum (= putamen + nucleus caudatus). Histologically these changes include vasodilatation, perivascular infiltrations of round cells and sometimes independent round cell foci, Nissl degeneration, sparse neuronophagia and degeneration of myelin sheaths. On the whole, the changes are not especially pronounced, not even in the acute fatal cases, and they are as a rule not massive but disseminated (Fig. 1).

In the chronic stage however, the patho-anatomical changes are more pronounced and severe. This stage is characterized by the extensive disappearance of nerve cells and glia scars within the cerebral parts affected (Fig. 2). The changes are often particularly marked within the substantia nigra. The normally dark coloured nucleus can become quite colourless, this is one of the positive macroscopic signs of chronic encephalitis. The pallidum may also sometimes appear macroscopically atrophic.

The individual clinical symptoms in the syndrome of encephalitis are naturally dependent upon the localization of the injuries within the brain. It may further be assumed that symptoms which often occur simultaneously have their patho-anatomical foundation in close topographic relation to each other. It was therefore natural that VON ECONOMO, and earlier MAUTHNER, believed that sleep disturbance was caused by injuries within the posterior part of the hypothalamus and the central grey matter round the anterior part of the aqueduct,

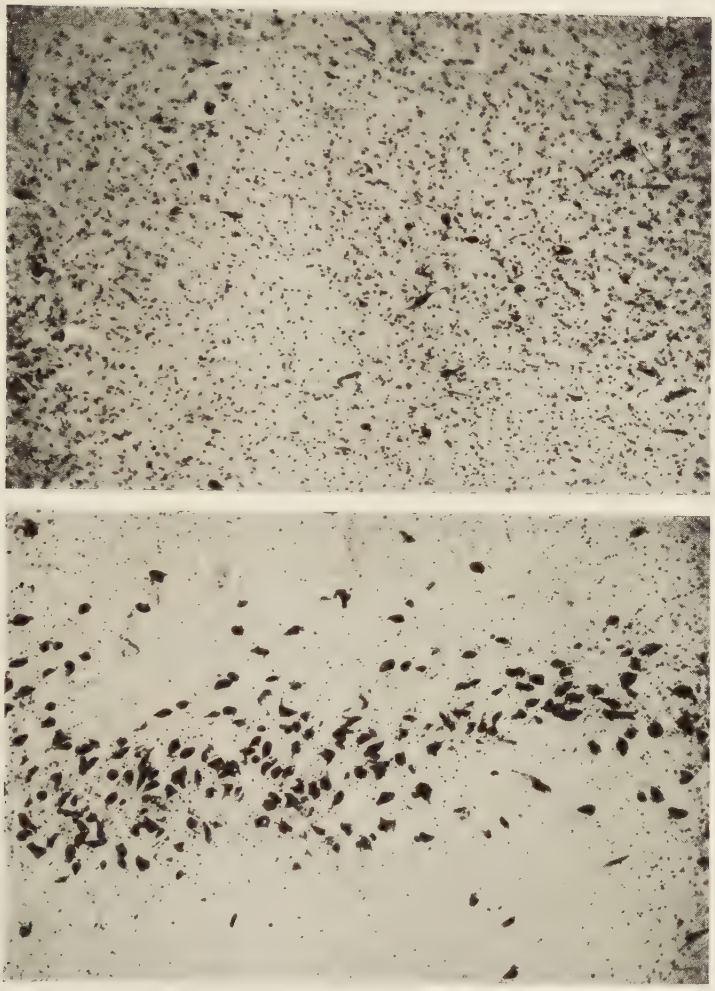

Fig. 2 (microphotographs, Nissl stain). The substantia nigra from a case of chronic encephalitis (above) showing pronounced disappearance of nerve cells and glia proliferation. The corresponding region from a normal substantia nigra (below) for the purpose of comparison.

just because of the oft recurring combination of oculo-motor symptoms and somnolence.

As a result of these investigations it became possible to speak of a *regulation centre for sleep-wakefulness* within the brain.

At first VON ECONOMO was of the opinion that the somnolence, in the acute phase of encephalitis lethargica, was due to injuries within the anterior part of the hypothalamus while hyposomnia

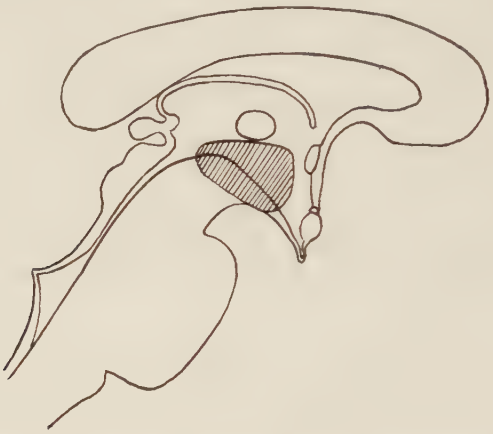

Fig. 3. The position of the sleep regulating centre according to von Economo's views.

originated from injuries within the posterior part. This led to the assumption of a sleep centre within the posterior part and a wakefulness centre within the anterior part of the hypothalamus. In his later publications he seems to have given up this idea and writes of a *sleep regulating centre* (»Schlafsteuerungszentrum») within the posterior part of the hypothalamus and anterior part of the grey matter round the aqueduct (Fig. 3).

In addition to encephalitis lethargica there are disturbances in the sleep regulation owing to other forms of encephalitis with similar localization of the inflammatory process, for instance, polioencephalitis haemorrhagica superior of GAYET-WERNICKE.

b. Narcolepsy.

Another disease or more correctly, syndrome, in which sleep disturbances are involved, is narcolepsy, first described by GELINEAU in 1880. The two cardinal symptoms to which the syndrome owes

its name, are sleep attacks which can be of varying duration but which are short as a rule, and cataplexy, frequently in the form of an affective loss of muscular tone. The fits of sleep vary in character from case to case. They may come on irresistably in connection with psychic and sensory stimuli of different kinds. They may also occur after meals, during monotonous occupations or they creep upon the individual when his attention is disengaged. Signs of parasympatheticotonia often accompany the sleep attacks, similar to those which can be observed during the physiological sleep. Magnussen (1942) has pointed out, for instance, that the temperature of the skin rises during the attacks as in physiological sleep. Also, between the attacks a tendency towards parasympatheticonia (or diminished sympathetic tonus) is displayed among narcoleptic subjects. Narcolepsy is combined with endocrine disturbances of various kinds to no small proportion of the cases, and it is known to occur during pregnancy. Some authors, for instance, Wilson (1928), maintain that the night sleep of narcoleptic persons is normal, while others (e. g. Cave 1931) have reported that in a high proportion of cases the night sleep is in reality disturbed in such a manner that the sleep is repeatedly interrupted, is rich in dreams sometimes with pavor nocturnus and somnambulism. In respect to narcolepsy in such cases Thiele & Bernhardt (1932) have published observations of a tendency towards transition from the normal monophasic to a polyphasic rhythm of sleep-wakefulness.

The syndrome of narcolepsy is often considered to be induced by an encephalitic process within the hypothalamic region. Other causes mentioned in the literature are, for instance, diminutive tumours within or adjacent to the hypothalamus, changes in the form of small pathological foci due to lues, arteriosclerosis or trauma of the skull (cf Daniels 1934). Some authors (e. g. Daniels) also believe in the existence of an idiopathic form of narcolepsy and finally there are descriptions of a familial form of the disease (Krabbe & Magnussen 1942). The patho-anatomical origin of the two last mentioned forms of narcolepsy is unknown as no histological investigation of such cases appears to have been described in the literature. Obscure is also the patho-physiology of narcolepsy owing to the fact that the physiological sleep mechanism is not yet elucidated.

c. Earlier animal experiments in sleep research.

Since von Economo pointed out the importance of the hypothalamic centres in respect to the sleep regulation a number of experiments have been made with test animals to verify the results of the human pathological investigations. The earliest experiments with this object in view consisted in injections of solutions of different substances in the hypothalamus (e. g. Demole 1927, Marinesco *et al.* 1929, Cloetta & Fischer 1930, Sahlgren 1934). Such injections often caused sleep for a shorter or longer period among animals. Berggren & Moberg (1929) as well as Marinesco (1929) showed however that the simple introduction of a cannula without injecting any fluid can produce sleep. For this reason, the results of such injectional tests, made with the aim of ascertaining a pharmacological effect, must be judged with great cautiousness, as the effect of the injection should be regarded as the result of mechanic and not chemic influence. On the other hand, the results serve as support for the assumption that a centre for sleep regulation lies within the hypothalamus.

Other pharmacological studies have also indicated the importance of the brain stem in respect to sleep regulation. These investigations will however be referred to in Chapter III.

As the patho-anatomical and experimental investigations described in the above account, strongly supported the assumption that a centre for sleep regulation is to be found within the posterior part of the hypothalamus, the older theories which counted with a more general collaboration on the part of the nervous system in the primary sleep regulation were put on one side. The localizatory part of the sleep problem had thus on the whole been solved. On the basis of the said investigations it has not been possible however to form any more exact diagnosis with regard to which cell group within the hypothalamus can presumably be the real centre for sleep regulation.

3. The function of the centre for sleep regulation.

After the patho-anatomical studies and some experimental investigations had indicated that a centre for sleep regulation exists within the hypothalamus, research began to concentrate upon the problem of the manner in which this centre functions.

a. Is the centre autonomous or not?

Research has given an apparently satisfactory answer to the question as to whether the hypothalamic centre is autonomous in respect to other parts of the central nervous system or whether it is only a factor, large, it is true, but of subordinate importance in the mechanism of sleep regulation. It has been observed that human monsters devoid of the cerebral hemispheres manifest, with regard to age, the ordinary type of diurnal cycle for sleep-wakefulness (cf GAMPER 1926). It has also been demonstrated in animal experiments with decortication that the cortex is not necessary for the regulation of sleep (e. g. KARPLUS & KREIDL 1914, ROTHMAN 1923).[1] Furthermore BREMER (1936) has reported that after cutting off the brain stem just behind the pons, the test animal displayed a typical alternation between sleep and wakefulness, as judged, among other things, from the electroencephalogram. These observations accordingly show that the regulation centre within the hypothalamus can function independently of nervous impulses from the cortex and the spinal cord. As a proof that impulses from the cranial nerves are not of vital importance to the sleep function either, it can be mentioned that individuals both blind and deaf display normal sleep regulation (KREIDL & HERZ 1924). As was earlier pointed out, it can be considered as out of question that any of the endocrine organs

[1] KLEITMAN, it is true, has maintained that such human monsters and decorticated experimental animals are devoid of sleep rhythm due to the fact that they are considered to be unable to keep awake. KLEITMAN seems to be supporting himself here on his own definition of sleep which states that sleep is characterized by "a loss of critical reactivity to events in one's environment." The qualification for "the critical reactivity" and consequently for the wakened condition, according to KLEITMAN, would be a retained cortical function. If however such an opinion is justifiable, there would be no possibility of a wakefulness state either in, for instance, the case of grave psychosis or idiocy where "the loss of *critical* reactivity" is constant. Evidently this is a question of definitions. So much can be said at least that in respect to the last mentioned conditions a monophasic sleep rhythm of a type characteristic for the human being can generally be observed. Even if individuals who are deficient in satisfactory cortical function are not supposed to have such a well endowed consciousness with regard to the surroundings as normal individuals, one cannot pronounce them destitute of a wakeful state on the whole.

or any other humoral factor should be superior in relation to the hypothalamus.

There should be justfication therefore in assuming that we are dealing with an at least to a certain extent autonomous centre for sleep regulation within the posterior part of the hypothalamus and the adjacent anterior part of the central grey matter of the mesencephalon. This centre should thus have its own rhythmic activity simultaneously as it is easily influenced by exo- and endogenous factors.

b. Is it a wakefulness or sleep centre?

Another and perhaps more important question is whether the centre within the hypothalamus is a *wakefulness centre* whose adequate activity is required to enable the individual to retain his wakeful condition, or if it is a *sleep centre* in the proper sense of the word, a centre whose enhanced activity produces sleep. The solution of this problem has afforded considerable difficulties and research has not succeeded in giving a definite answer to this question either.

The two workers who, on the basis of patho-anatomical investigations, localized the centre for sleep regulation, entertained quite opposite views in respect to this question. Then Mauthner came forward with a theory of the physiological sleep regulation which implies that sleep is caused by exhaustion of the periventricular grey matter. This exhaustion is supposed to bring about a blockade of the centrifugal impulses from, and the centripetal impulses to the cerebral cortex. Mauthner consequently assumed the hypothalamic centre to be a *wakefulness centre*. Viewed as a whole however his theory must be faulty, as it has long been known that neither centrifugal nor centripetal pathways between the cortex and various parts of the body run through the hypothalamus.

Von Economo (1930) on the other hand considers that fatigue toxins of the hypnotoxin type (Piéron) stimulate the hypothalamic centre to active inhibition of the thalamic and cortical functions (involving what von Economo calls "brain sleep"). He also presumes active influences on other vegetative functions so that the vegetative condition of the whole organism is changed to that which is the characteristic type for physiological sleep (and according

to von Economo "body sleep" sets in). In divergence from Mauthner, von Economo views the centre as a *sleep centre.*

It was obvious however that patho-anatomical studies alone could give no reliable answer to the question respecting the mode of function of the regulation centre. It implied making the hypothalamic regions available for intervention of various kinds, with the aid of experimental animals. The injection tests, as earlier seen (p. 18), proved to be less suitable in these respects. As will be observed in the following, the physiologists also found themselves divided into two parties in regard to the all important question: wakefulness or sleep centre?

Of fundamental significance for the above mentioned question are the experiments of Hess (1928, 1932) with electric stimulation of the hypothalamic region. He worked out a method for inserting filiform electrodes into the brain of the experimental animal (cat) and with this method is was also possible to fasten the electrodes to the roof of the skull. When the electrodes were insulated, with the exception of the point, the current was led from one point to another. Hess employed a pulsating direct current at a strength of some mA. The animal who was allowed to wake up after the operation could move freely with thin wires attached to the inserted electrodes. When the feeble current passed through the parts of the brain in question, the animal manifested all the signs of normal falling asleep. The animal slept the whole time as long as the current was passing. When the current was switched off it wakened spontaneously after a while. Hess was of the opinion that the type of current used had a stimulating effect upon the parts of the brain where it was employed, and this due to the fact that this type of pulsating direct current, according to his earlier experiences, proved to have a stimulating effect on other parts of the nervous system. The weakest currents produced sleep if the points of the electrodes were inserted within the hypothalamic region, in the neighbourhood of the third ventricle. Owing to these results Hess believes that the centre by reason of the enhanced activity produces sleep, that is to say, he presumes it a real *sleep centre.* Earlier, Hess had shown that intraventricular injections of the parasympathetic stimulant choline and of ergotamine, with its paralysing effect on the sympatic, could induce sleep in animals. For this reason, he explains sleep as a result of a general vegetative

reversal to a condition of parasympatheticotonia and of an active inhibition within the "animal" nervous system (animal in contrast to vegetative). Hess accordingly appears to consider the hypothalamic region as a main organ in the parasympathetic system. The vegetative phenomena in sleep he assumes to be caused by increased activity within a similar parasympathetic primary organ. Kleitman expresses these phenomena "concomitants of sleep" including changes in the circulation, respiration and temperature, within different parts of the metabolism, in muscular tone etc. It is a known fact that just within the hypothalamic regions there exist regulating centres for the vegetative-endocrine functions, but as to how these centres affect the respective functions is still far from satisfactorily elucidated.

Agerberg (1942) has arrived at a theory for the sleep regulation which is somewhat akin to the explanation given by Hess. He postulates sleep as the result of an inner inhibition. This he considers to have been brought about by the sympathetic subdivision of the vegetative nervous system which, through exhaustion during the period of wakefulness, becomes refractory towards the impulses conveyed via the animal nervous system. Agerberg assumes moreover that the impulses of the inner inhibition mainly proceed from the parasympatic. Accordingly he, also, counts with a *sleep centre*.

Ranson (1934, 1939) has come to quite the opposite conclusion to Hess as a result of experiments with tissue injury to the brain stem. He employed the *Horsley-Clark stereotaxic instrument* when inserting the electrode. After producing small bilateral electrolytic lesions within the hypothalamus of cats and monkeys there was a sleep effect of some days duration, which effect seems to have been induced due to the necroses being placed so that the tractus mamillothalamicus and corpora mamillaria were injured. In consequence of these results Ranson and also his co-worker Harrison (1940) maintain that an intact hypothalamic function is necessary in order to retain consciousness. His opinion thus is that the centre for sleep regulation is to be regarded as a *wakefulness centre*. The said authors also believe that the symptoms of parasympatheticotonia during sleep is not due to enhanced parasympathetic tone but rather to reduced sympatheticotonia. Experimental reports on the matter indicate that in their endevour to reproduce Hess' tests, the result was not sleep, but a stage of sympathetic irritation ("sham rage"),

when a weak pulsating direct current was allowed to influence the hypothalamic region.

In his extensive monograph on the sleep problem KLEITMAN arrives at what he calls an "evolutionary theory of sleep" which can most easily be summed up with his own words: "Wakefulness of necessity is a subcortical, probably hypothalamic function, whereas supplimentary 'wakefulness of choice' as well as the diurnal sleep-wakefulness cycle is a cortical function." Thus KLEITMAN also counts with a *wakefulness centre* within the hypothalamus.

MAGNUSSEN (1942) has accepted RANSON's views. He describes the sleep regulation as rhythmic variations in the activity of a *wakefulness centre* within the hypothalamic regions. In the event of under-function of this centre, the sympathetic impulses which keep the individual awake are diminished or they cease, and the individual finds himself in a state of vegetative sleep-preparedness. This condition promotes the sleep which is presumably caused by a blockade of the afferent pathways in the thalamus region.

Animal experiments with temperature measurements within various parts of the brain have been performed with the aim of elucidation the important question: wakefulness or sleep centre? SEROTA (1939) inserted filiform thermo-elements both into the hypothalamus and in the cortex. On this occasion it was verified that in a state of wakefulness the temperature of the hypothalamus was 0.1°—0.5° C higher than in the cortex. When the animal slept, the temperature decreased in both of the investigated parts of the brain. The decrease was greater within the hypothalamus than within the cortex so that the difference between the two regions was 0.1°—0.2° C less than during wakefulness. Owing to the tests being made with heated electrodes, SEROTA was of the opinon that he had precluded the possibility that the decrease of temperature within hypothalamus should be due to changes of the circulation intensity. As a result of his experiments he came to the conclusion that the hypothalamus during sleep is less active than in a state of wakefulness. In other words he postulates that the centre is to be understood as a *wakefulness centre.*

In similar tests FEITELBERG & LAMPL (1939) have found that under the influence of barbital, temperature conditions within the grey matter of the entire brain stem coincide with those respecting the hypothalamus, which SEROTA published. This circumstance di-

minishes the demonstrative value of Serota's interpretation. Possible temperature changes within the small hypothalamus region due to changes of activity may be leveled by the decrease of temperature within the surrounding voluminous parts of the brain stem.

In summing up it can be said that the experimental sleep research which refers to the hypothalamic region has given further support to the assumption that a centre for sleep regulation is to be found within this part of the brain. The question as to how this centre functions still remains open however. A discussion of the apparently paradoxical circumstance that stimulation as well as injury within the hypothalamic regulation centre produces the same effect, namely sleep, is to be deferred in this connection however, but will be taken up in the discussion with respect to the author's own results from experiments on tissue injury within the hypothalamic regions (Chapter II).

c. The sleep-intermediatory effector organs of the hypothalamic centre for sleep regulation.

A third question is by what mechanism does the hypothalamic centre produce sleep. Mauthner, as previously stated, maintained the existence of a blockade of afferent and efferent impulses within the centre itself. Recent authors are of the opinion however that the centre works through influences on other parts of the brain and even on other organs. Few investigations have been made which can directly elucidate this part of the sleep problem. In this discussion it is the thalamus[1] above all, which is supposed to be under

[1] It should also be pointed out in this connection that a number of authors have shown a disposition to supersede the hypothalamus as sleep regulating centre by the thalamus (ref. by Harrison 1940). Trömner (1928) was the first and perhaps the most energetic advocate of such an assumption. Spiegel & Inaba (1927) consider themselves able to give experimental verification in this respect. These authors did not succeed in producing sleep among test animals (rabbits and dogs) by means of one-sided puncturing of the hypothalamus nor through total (?) destruction of the periventricular grey substance of rabbits. On the other hand, they achieved a permanent condition of disturbance in the consciousness after diffuse bilateral tissue injury within the thalamus of dogs. Whether this disturbance, in accordance with the view of Spiegel & Inaba, can be characterized as sleep, or not, is problematic (cf Kleitman), but the observation is of interest, inasmuch as it indicates

the influence of the hypothalamus as regards the sleep function. This particular part of the brain is mentioned in this connection because it constitutes a rallying point for the sensory pathways, and because the perceptibility of the impulses mediated in these pathways is severely reduced or else suspended during sleep. The vegetative-endocrine centres within the brain stem must also be assumed to be influenced by the centre for sleep regulation because of the changes of vegetative functions and metabolism, furthermore the extra-pyramidal system due to the changes of muscular tone during sleep.

* *
*

The development of sleep research during the most recent decades has led to an almost general acceptance of the view that a more or less autonomous centre for sleep regulation is to be found within the hypothalamus. The problem: wakefulness or sleep centre? is still awaiting its solution. The reasons for the two different lines of opinions as represented in the literature appear almost equally good. If however one favours the one assumption, it seems difficult to give a resonable explanation of the experiences which support the opposite view. With reference to the results put forward, and with the prevalent opinion of the mode of action of nervous tissue, the possibility of arriving at any logical explanation of the physiological cause of sleep regulation would seem very remote.

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that an intact thalamic function seems to be of importance to the preservation of consciousness. Basing himself on these results SPIEGEL (1927) assumes that sleep should be due, either to the inability of the cortex, being in a refractory period, to constitute the thalamic impulses to consciousness, or to inhibition of the function of the thalamus due to impulses from the cortex.

CHAPTER II.

The sleep effect of hypothalamic electrolytic lesions.

The hypothalamus is no sharply demarcated part of the brain. In his "Anatomy of the nervous system" RANSON gives the following definition of this region. "The hypothalamus lies ventral to the thalamus and forms the floor and parts of the lateral wall of the third ventricle. As seen on the ventral surface of the brain it includes the optic chiasma, corpora mamillaria, tuber cinereum, infundibulum and neurohypophysis." Thus, broadly seen, the hypothalamus may be said to comprise the parts of the brain adjacent to the lowest part of the third ventricle. With slight delimitation it merges backwards into the grey matter surrounding the aqueductus Sylvii within the mesencephalon. No essential differences between the extent and relative size of the hypothalamus of the human being, cat and rabbit have been specified as far as is known.

It is obvious that this part of the brain is difficult to get at for localized experimental purposes as it lies right above the central part of the base of the skull. With reference to experimental sleep research and the study of the hypothalamic functions on the whole, two methods have hitherto been chiefly made use of for directly investigating the parts of the brain in question, the one which HESS worked out and the one which is based on the *Horsley-Clark instrument*.

HESS has described his method in a particularly exhaustive work (1932). In brief, a diminutive electrode-holder is fixed on the top of the animal's head (Fig. 4). The electrodes, in the form of thin metal wires were inserted through small openings in the skull into the brain tissue until the tips reached the stipulated spot, whereupon they were attached to the holder. The great advantage of this method

is that the animal, with no further arrangement, after the operation, can move freely with thin leads attached to the electrodes protruding from the skull. It is accordingly particularly suited to stimulation tests. A successful result of an operation however can only be achieved with animals of the same race and of similar size because the electrode-holder is adjusted only to one type and size of skull. The method accordingly has one disadvantage, the animal material must be selected and moreover, the individual variations in the structure of the animal's head, although they be small, will undoubtedly occur also within the chosen material, and this must tend to render difficult the localization technic.

The other method which works with the *Horsley-Clark stereotaxic instrument,* and which is employed by Ranson and many others (Horsley & Clark 1905, Harrison 1938, Fig. 5), is scarcely adapted to stimulation tests. On the other hand, it is more adapted to experiments with electrolytic lesions within different parts of the brain. The instrument is fixed to the head of the animal, and with the aid of a manipulator, the electrode is gradually inserted until the tip comes into contact with the desired spot. The appointed placing is calculated as starting from certain external points of the skeleton on the animal's cranium, the situation of which, in relation to the different parts of the brain, is judged from experience. This method also obviously demands a thorough knowledge and experience concerning the dimensions of the animal's cranium and would seem complicated with reference to the individual variations in the structure of the cranium.

1. The X-ray stereotaxic instrument.

In order to avoid the inconveniences incident to the two methods described above, the author has worked out a method in which the effect of the individual variations in the anatomical conditions of the experimental animals is largely eliminated.

The main principle of this method is that the localization is done with the aid of X-ray photography.

A smaller mobile head clamp can be inserted in and attached to a main apparatus, mounted on the operation table. The latter apparatus carries on one side a mica plate with an X-ray tight coordinate system in $^1/_2$ cm, also, outside, a plate-holder. On the

other side of the main apparatus there is an X-ray apparatus so placed that its central pencil of rays coincides with the origo of the above mentioned coordinate system. Above the crown of the animal's head is a manipulator for inserting the electrodes. This manipulator is mobile along the slides of the main apparatus, in every dimension. The scales on these slides correspond to the coordinate system of the mica plate. The appearance of the instrument is illustrated by Figs. 6—10.

The course of the operative intervention is as follows. The fur of the animal's crown is removed, the animal is anesthetized and placed on the operation table. The head is fixed in the head clamp which then is pushed along rails into the main apparatus, where the clamp is screwed fast. The head should be so placed that the part to be operated lies as near as possible to the central pencil of the X-rays. A symmetrical position of the head in the apparatus is also desirable. The adjustment vertically can be done by raising or lowering the animal's nose in the head clamp and by exchanging the detachable bottom plate of this clamp for one, thicker or thinner, as the case may be.

When the animal's head has come into place an X-ray photograph is taken of its skull. On the film will be seen the central part of the animal's head in profile and the coordinate system (Figs. 11 and 12). In this connection some important skeleton details can easily be discerned, the dorsum sellae and the boundary lines between the anterior, central and posterior cranial cavities. These boundary lines are of significance in that a coincidence of the lines on the two sides shows that the position of the head is satisfactory. The dorsum sellae is the starting point for the localization within the brain stem. Its situation in relation to the hypothalamus can be seen from the schematic outlines in Figs. 11 and 12. A little mark is made on the film at the point which assumably corresponds to the position of the part of the brain which the tip of the electrode is about to contact. The position of this mark vertically and horisontally in relation to the origo of the coordinate system is calculated in mm.

Subsequently the operative intervention begins. A median incision is made in the skin in the centre of the animal's crown and the periosteum of one or two cm^2 is removed. The manipulator is moved along its axes to a point which corresponds to the deviation

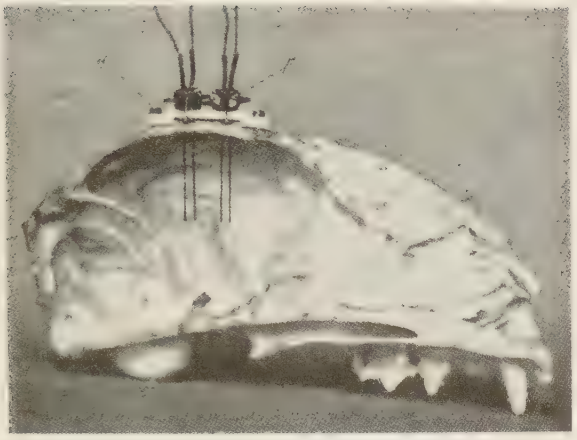


Fig. 4. The method of HESS. The little electrode-holder fixed with screws on the roof of the animal's skull (cat). The electrodes inserted into the cavity of the skull. (From HESS 1932.)

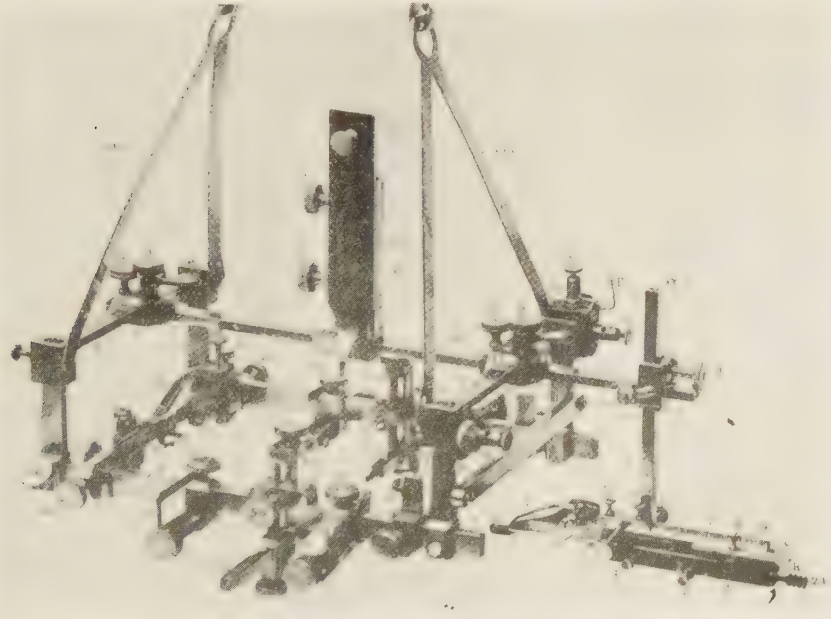


Fig. 5. The Horsley-Clark stereotaxic instrument (from HORSLEY & CLARK 1905). The instrument used by RANSON et al. is somewhat modified (cf HARRISON 1938), but in principle the method is the same.

Fig. 6.

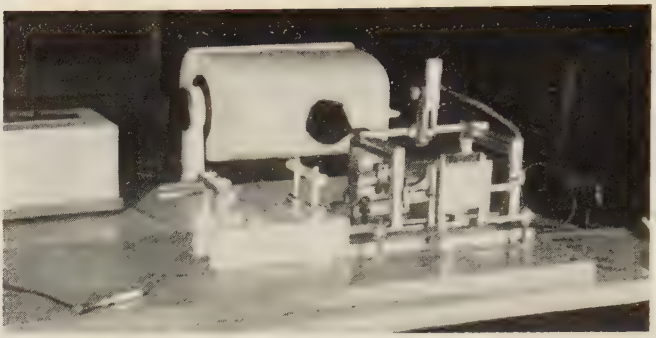


Fig. 7.

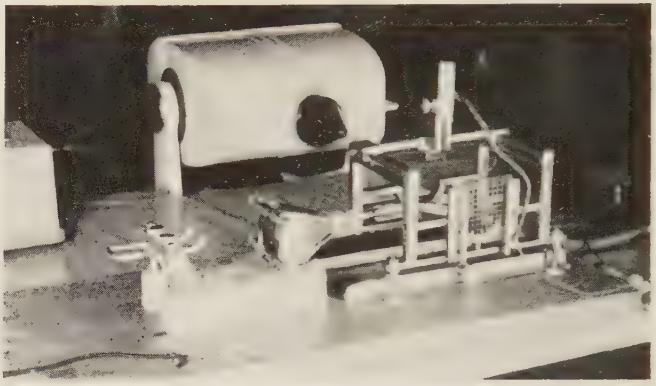


Fig. 8.

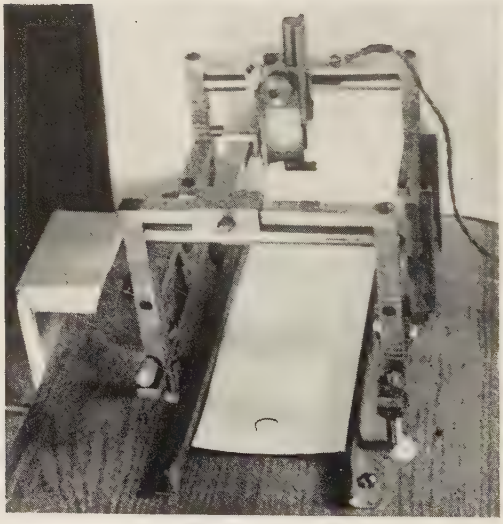


Fig. 9.

Fig. 10.

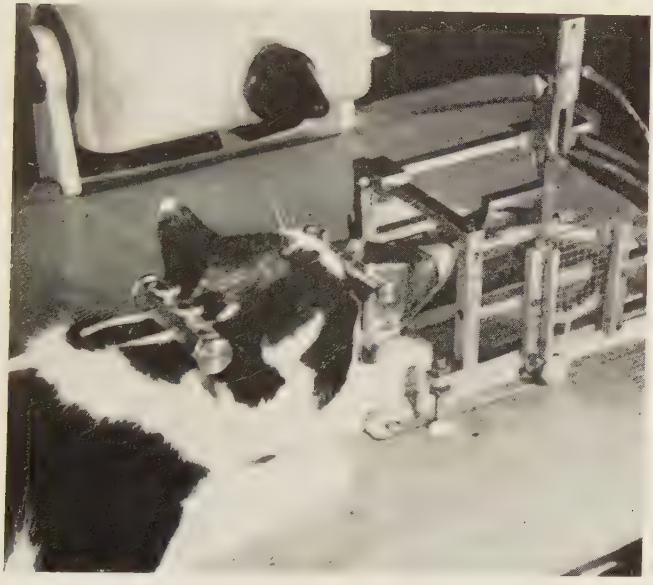


Fig. 6—10. The X-ray stereotaxic instrument. In Figs. 6 and 9 the instrument is arranged for injectional anesthesia, in Figs. 7 and 10 for inhalational anesthesia with the gas-funnel fixed to the head-clamp. Fig. 8 shows the electrode manipulator; on each side of the screw there is a scale, the left one indicates the situation of the manipulator in regard to the main apparatus, on the right one is read the situation of the electrode in regard to the manipulator.

Fig. 11–12. X-ray photographs of the central part of a cat's (left) and a rabbit's (right) head. The pointer marks the dorsum sellae from which the clivus runs down to the left. The origo of the coordinate system is marked with a little ring (of X-ray tight metal). Schematic figures of the sella tursica and its situation in relation to the hypothalamus for the purpose of comparison. (The X-ray photographs are somewhat retouched, especially the coordinate system, in order to guarantee the demonstration of the principles of the method.)

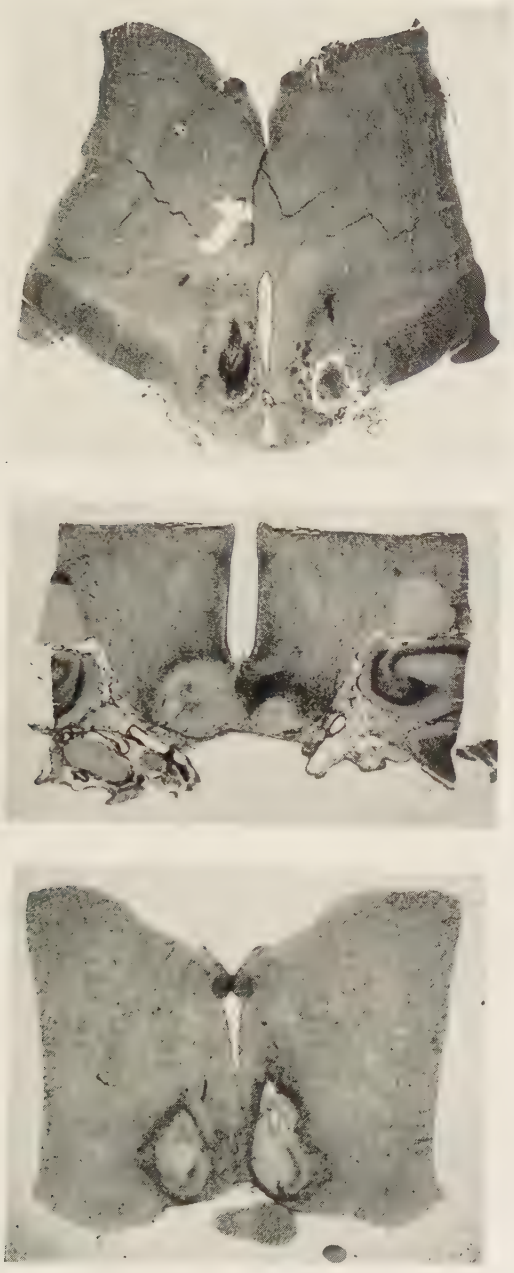


Fig. 13 (microphotographs, low power magnification, Nissl stain). Bilateral hypothalamic electrolytic lesions in cats (Cases 19, 38 and 41).

Fig. 14 (microphotographs, low power magnification, Nissl stain). Bilateral hypothalamic electrolytic lesions in rabbits. No sleep effect.

sideways from the origo read off on the X-ray film. A small mark is placed in the bone 1.5—2 mm laterally of the middle line which is indicated by the sutura sagittalis. The manipulator is moved to the side and a trepan hole of 1—2 mm in diameter is made with a drill. One should strive not to perforate the dura. Eventual bleeding from the bone is stopped with a tamponade for a minute or so.

The electrodes employed have been 0.35—0.40 mm thick and are made of stainless steel. They are insulated by means of a durable lacquer, with the exception of one mm at the tip.

The electrode needle is attached to the manipulator which is placed right above the trepan hole. By slowly turning the screw of the manipulator the electrode is conducted through the dura and down into the cerebral tissue. On the scales of the manipulator can be read when the tip of the needle has reached the point which corresponds to the mark on the X-ray film. If the animal's head is symmetrically placed in the apparatus, the tip of the needle will be situated as far from the median plane as the trepan hole is laterally of the sutura sagittalis.

For the electrolysis a galvanic battery and a milliammètre are used. A brass rod inserted within the animal's rectum serves as an indifferent electrode. The neddle is suitably connected with the anode of the battery. In order to bring about a necrosis of 1.5—2 mm in diameter, as Harrison has pointed out, a current of about 3 mA is required which is allowed to act for one minute. During the stipulated experimental conditions this current is obtained with a potential of 6—9 volts. A regulative resistance (50 000 ohms) is introduced in the circuit in order to able successively to increase the intensity of the current to the desired level. If the entire intensity of 3 mA be immediately released through the animal, when the current is switched on, the animal often reacts with fairly vigorous movements, which are liable to displace the position of the head in the clamp. If on the other hand, the intensity of the current is slowly increased up to 3 mA, these disturbances are nearly always avoided. When the current, after having reached the said intensity, is allowed to act for one minute, it is switched off, which can be done without any inconvenience direct from 3 mA. The electrode is then slowly withdrawn from the animal's head. In this way a number of electrolyses can be performed at one and the same operation. The trepan holes are closed with wax and the wound is sutured.

The animal is removed from the apparatus and placed in a cage for further observation.

The tissue injury is in these experiments evidently due to an electrolytic effect, that is to say, the current causes a change within the composition of electrolytes, which is incompatible with cellular life. During the first day after the operation the general tissue structure is well preserved, there is however marked Nissl degeneration and increasing decomposition of nuclear chromatine and slight localized edema. Within two days after the operation there developed a total necrosis of the tissue with slight reaction in the adjacent surroundings in the form of solitary round cells. During the next days appear, sometimes abundantly, fat-laden phagocytes at the edge of the necrosis. In later stages, i. e. after some months, the necrosis is resorbed and replaced by a cicatrical tissue of glia.

2. The course of the sleep effect.

To begin with the method of operation was worked out with *rabbits* as experimental animals. A derivative of barbituric acid, *numal* (allylisopropyle-barbituric acid, Hoffman la Roche) was used as the anesthetic. It was seen that, in some 10 tests, the animals wakened up after the operation, at about the same time (12—16 hours) as is usual with the anesthesia, even though no operation had taken place. At a number of later experiments with rabbits, *amytal* (isoamyl-ethyl-barbituric acid) was used instead of *numal*. *Amytal* in dosage giving a satisfactorily deep anesthesia, gives a considerably shorter one of about 2 hours. There were 7 tests, and in each, two similarly heavy rabbits received the same amount of anesthetic. It was found also here that the bilateral electrolytic lesions within the posterior part of the hypothalamus (histologically verified; cf Fig. 14), had not positively changed the duration of the anesthesia either one way or another. The operation consequently involves no sleep effect on the cessation of the anesthesia, that is to say, $^3/_4$—1 hour after the electrolysis. Moreover, it seems improbable that a sleep effect of short duration could conceal itself in the brief post-operative anesthesia. For this reason *it seems impossible to achieve any sleep effect with rabbits as experimental animals by means of bilateral electrolytic necrotisation within the posterior part of the hypothalamus.*

With *cats* as test objects the observations of earlier authors could be reproduced even at the first experiments. The animals slept for some days after a successful operation, and then wakened up. The post-operative anesthesia thus merged without delimitation into a condition of sleep. In Table I the results of some of these experiments are elucidated.

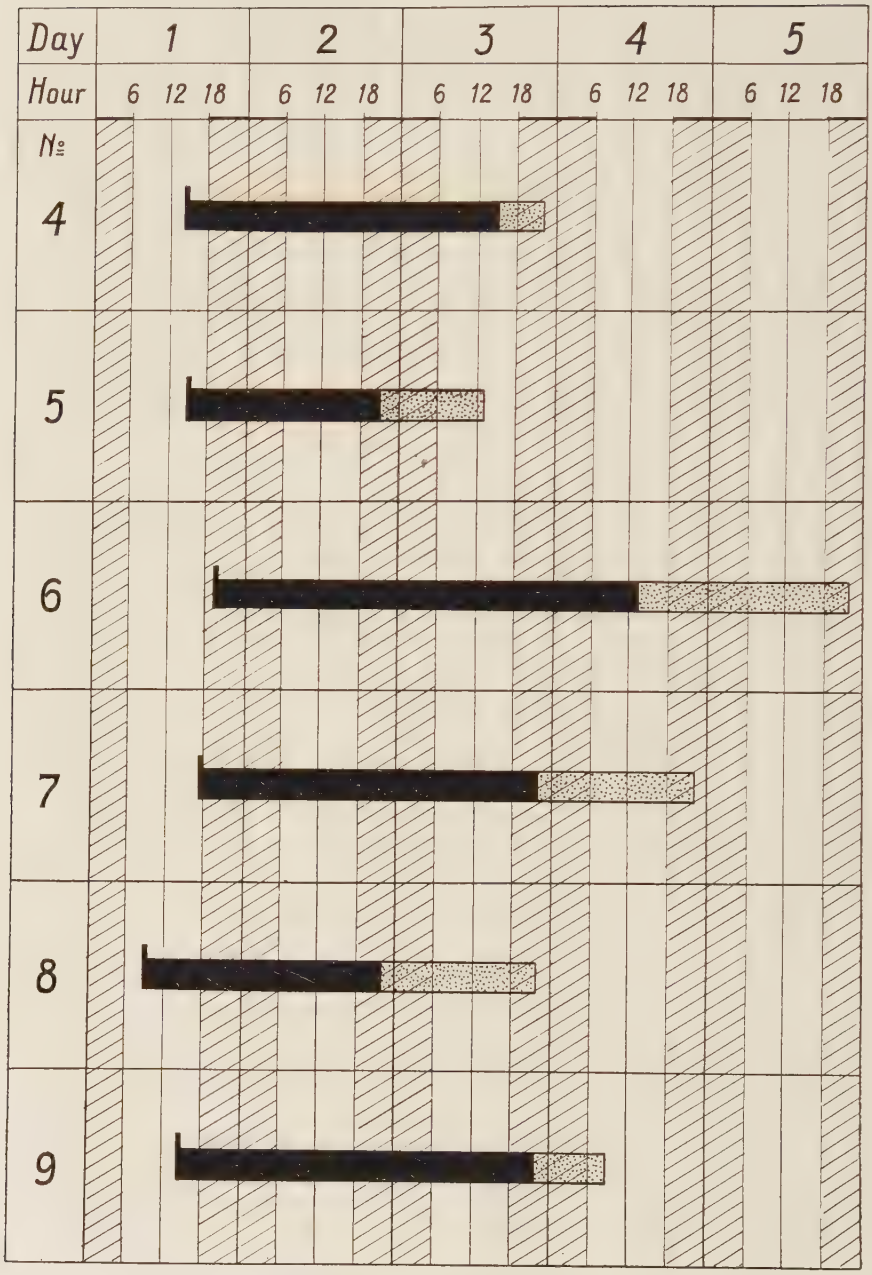
In this Table I and later also in Table II, somnolence is indicated by ■ and sleep by ▦. A state of pronounced apathy is reckoned as somnolence. In this event, the animal lies still in his cage and loses the ordinary quick reaction and attentiveness to its surroundings. When the animal slept continously the state was regarded as sleep. The term has had to be employed also for those cases when the animal temporarily wakened up owing to disturbances in the surroundings but slept again when everything was quiet. Of course these terms are schematic when the demarcations between wakefulness, somnolence and sleep are quite diffuse. With the above given distinctions it is frequently difficult to determine in the individual case how the actual condition shall be characterized.

Observations of the animal have been made during the post-operative course with short intervals of $^1/_2$—1 hour throughout the day from 8 o'clock to 23. The nightly observations have been restricted to the night immediately following the operation when the interval, free from observation, was between 1 o'clock and 7. If the condition revealed change from somnolence to sleep, between the last observation on the evening and the first observation in the morning, sleep has been assumed to begin on the latter occasion. Should sleep however have merged into somnolence during the observation-free interval, then the indication 'sleep' had ceased on the earlier occasion.

Finally the results of the subsequent histological investigation of the extent of the injuries are schematically collected in the Tables. After the fixation of the brain in formaline the anterior part of the brain stem was removed in one piece and embedded in paraffin. The stem was then cut into a series of sections and each 10th section (20 μ) was coloured with Nissl stain.

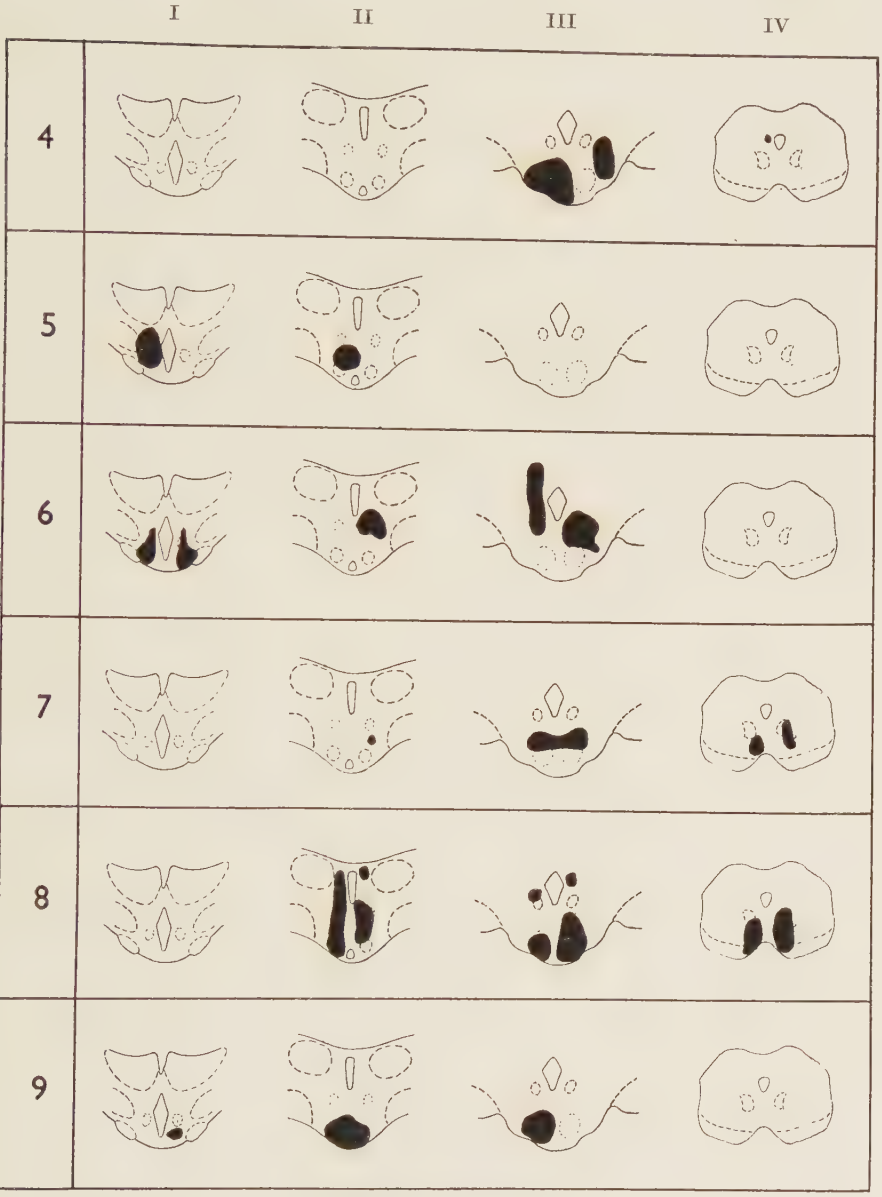
The anesthetic *numal* involved a considerable inconvenience however in that all observations were rendered impossible during the greater part of the first 24 hours after the operation, that is to say, during the time the effect of the anesthesia remained. With the intention of obtaining some idea as to the immediate effect of hypothalamic electrolytic lesions *nitrous oxide* (N_2O) was employed in the later tests instead of *numal*. The animal can be wakened up from the anesthesia with this gas some minutes after the gas ceased to be supplied.

TABLE I.



Cat 4 killed 3.5 months after operation (a. op.). Cat 5 killed 6 days a. op. Cat 6 dead 9 days a. op. Cat 7 killed 5 months a. op. Cat 8 killed 6 days a. op. Cat 9 killed 4 days a. op.

I. Transverse section through the brain stem at the boundary between the anterior and posterior parts of the hypothalamus. II. Section through the anterior part of the corpora mamillaria. III. Section through the corpora mamillaria. IV. Section through the anterior part of the mesencephalon.



The method of administration was as follows. The cat is conveyed to a box with a hole at the short end between the lid and the under part, sufficiently large for the animal's neck. The anesthesia is induced by administering the gas with the aid of an ordinary glass funnel which is coupled to a rubber tube direct from a gas cylinder. When the animal has reached a satisfactory depth of anesthesia it is transferred to the operation table by the scruff of the neck while the glass funnel with the gas is kept before the nose. The animal's head is placed in the head clamp, the funnel is removed and the anesthesia proceeds, the gas cylinder having been attached to another tube which discharges into a funnel fixed to the head clamp before the animal's nose (Fig. 7). As the funnel does not fit closely round the animal's nose, the gas becomes mixed with air to a satisfactory degree and thus asphyxia is prevented. The tendency of the animal to wake up, especially in the earlier stages of the anesthesia, as well as the tendency towards respiratory arrest due to anoxemia has to be controlled in the individual case by a carefully measured administration of gas. The arrest of respiration which is foreboded by a series of hasty and deep respiratory movements, and later by general tonic convulsion in the whole body can, in the majority of cases, be relieved through disconnecting the gas supply and by energetically applying artificial respiration while the animal still lies in the instrument. At the time of the electrolysis the supply of gas was usually somewhat increased in order to prevent parrying movements. This method of anesthesia has only been used in experiments with cats. Rabbits have proved to be very difficult to anesthetize by the above method.

As with regard to the effect of the operation on sleep regulation no extra-ordinary variations took place, it would seem unnecessary to occupy space here with a complete experiment protocol for every case. A schematic survey of these tests will be given in Table II.

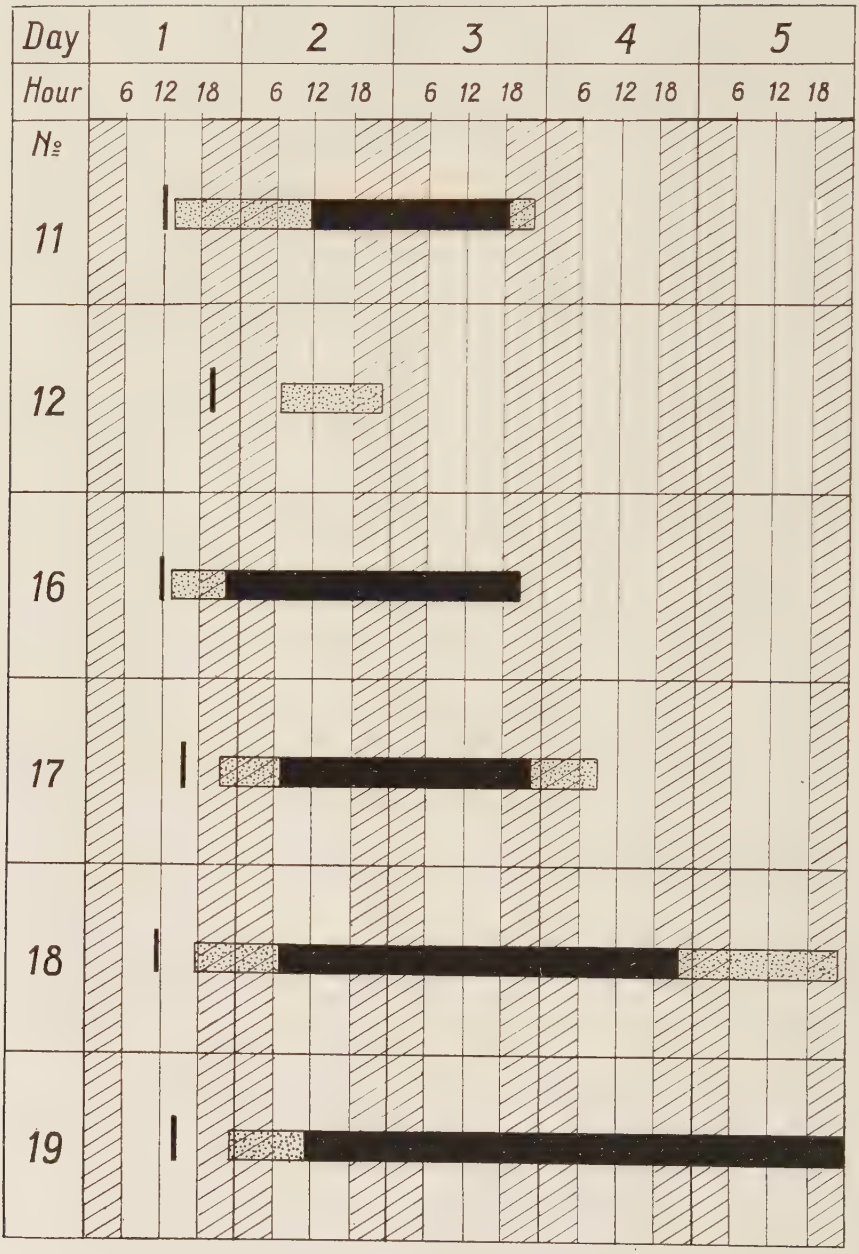
The employment of nitrous oxide has thus rendered it possible to form an idea of the experimental animal's behaviour even during the time closely following the operation. Usually the gas supply has ceased immediately after the last electrolysis. The animal has then had the possibility of waking up out of the anesthesia during the short time requisite for closing the openings in the skull and suturing the wound. The observation was then made that *the animals, without exception, wakened up from the anesthesia in what seemed to be a fully normal manner.* They were awake and behaved quite ordinarily for some hours (cf Table II), upon which they gradually become apathetic and somnolent, to finally fall asleep. When the animals became somnolent they laid themselves down in a corner of the cage. To begin with they had then mostly placed

themselves in the ordinary position of repose with all their paws under the body, but later, at the onset of sleep they either lay in the characteristic curled-up position or they lay outstretched on the one side. The sleep was calm, the breathing regular and slow. The depth of sleep varied considerably. Sometimes it was easy to wake the animal and then it could be done with fairly slight stimulus. In other cases the animal was wakened with difficulty. Only by lifting it up in a standing position could it be made to go a few steps but even then it almost immediately laid itself down and rapidly fell asleep again. The animal's movements have often been considerably incoordinated on these occasions. Variations in the duration of the periods of sleep are to be seen from Table II. After some twenty four hours of incessant somnolence the animals finally wakened up again. The sleep following the operation had thus essentially the same characteristics as that which was earlier described in literature in connection with tests as to the influence of various forms of intervention on the hypothalamus.

It is readily understandable that the necroses which are small in themselves, but, large in comparison with the hypothalamus region, render it more or less impossible to undertake any subtle analyses as to which of the cell groups must be destroyed in order to obtain a sleep effect and, accordingly, which shall be indicated as the real centre for sleep regulation. With this method, and undoubtedly with every other the possibility must be excluded of selectively destroying one single functionally unitary cell group which need not be anatomically defined. The only fact which can be deduced with respect to the localization of electrolytic lesions in correlation with the sleep effect, is that the operation must be performed within the posterior part of the hypothalamus. The tests in which the injuries occurred for some reason or other outside this limited region, might be regarded as controls indicating the fact, earlier mentioned in the literature, that sleep effect cannot be achieved after similar tissue destructions within other cerebral regions than just the posterior part of the hypothalamus.

The electrolysis must be performed bilaterally as is pointed out in the literature (cf Ranson). In some of the above tabulated experiments however the necroses were chiefly situated unilaterally and only extend slightly over the median plane and, non the less, sleep effect occurred. Complete unilateral electrolysis never induced sleep.

TABLE II.



Cat 11 killed 2 days a. op. Cat 12 killed 2 days a. op. Cat 16 dead 2 days a. op. Cat 17 killed 3 months a. op. Cat 18 dead 7 days a. op. Cat 19 killed 14 days a. op. (sleep also the 6th day a. op., somnolence the 7th, afterwards awake).

I. Transverse section through the brain stem at the boundary between the anterior and posterior parts of the hypothalamus. II. Section through the anterior part of the corpora mamillaria. III. Section through the corpora mamillaria. IV. Section through the anterior part of the mesencephalon.

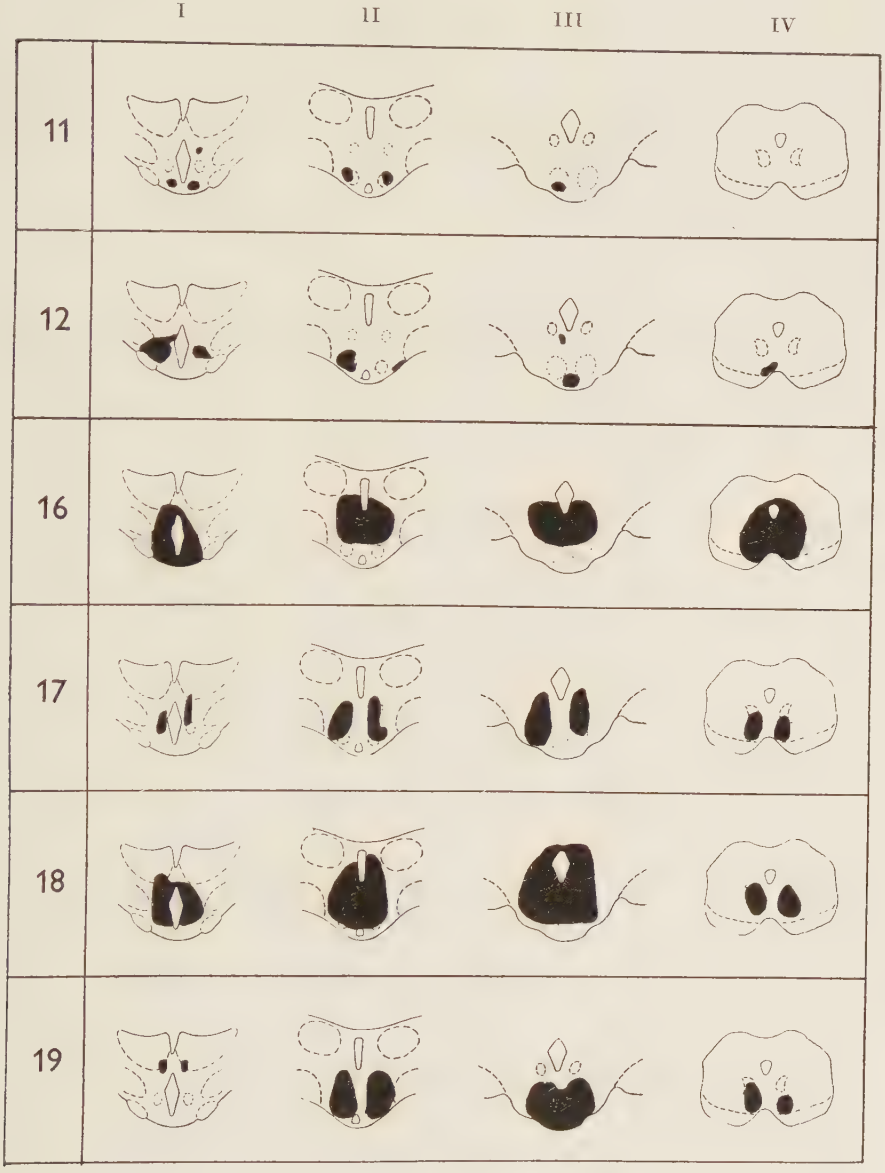
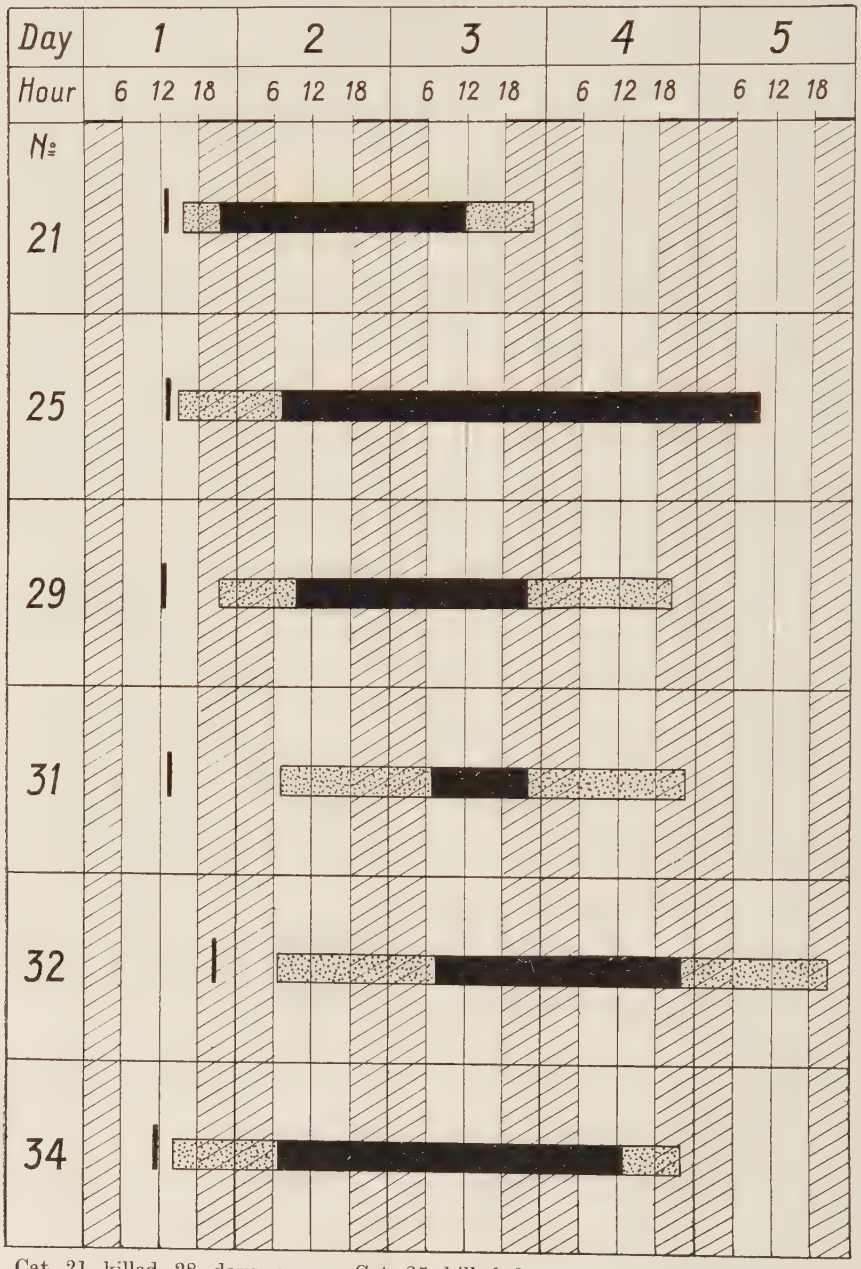


TABLE II (cont.).



Cat 21 killed 28 days a. op. Cat 25 killed 1 year a. op. Cat 29 dead 11 days a. op. Cat 31 dead 11 days a. op. Cat 32 dead 7 days a. op. Cat 34 dead 16 days a. op.

I. Transverse section through the brain stem at the boundary between the anterior and posterior parts of the hypothalamus. II. Section through the anterior part of the corpora mamillaria. III. Section through the corpora mamillaria. IV. Section through the anterior part of the mesencephalon.

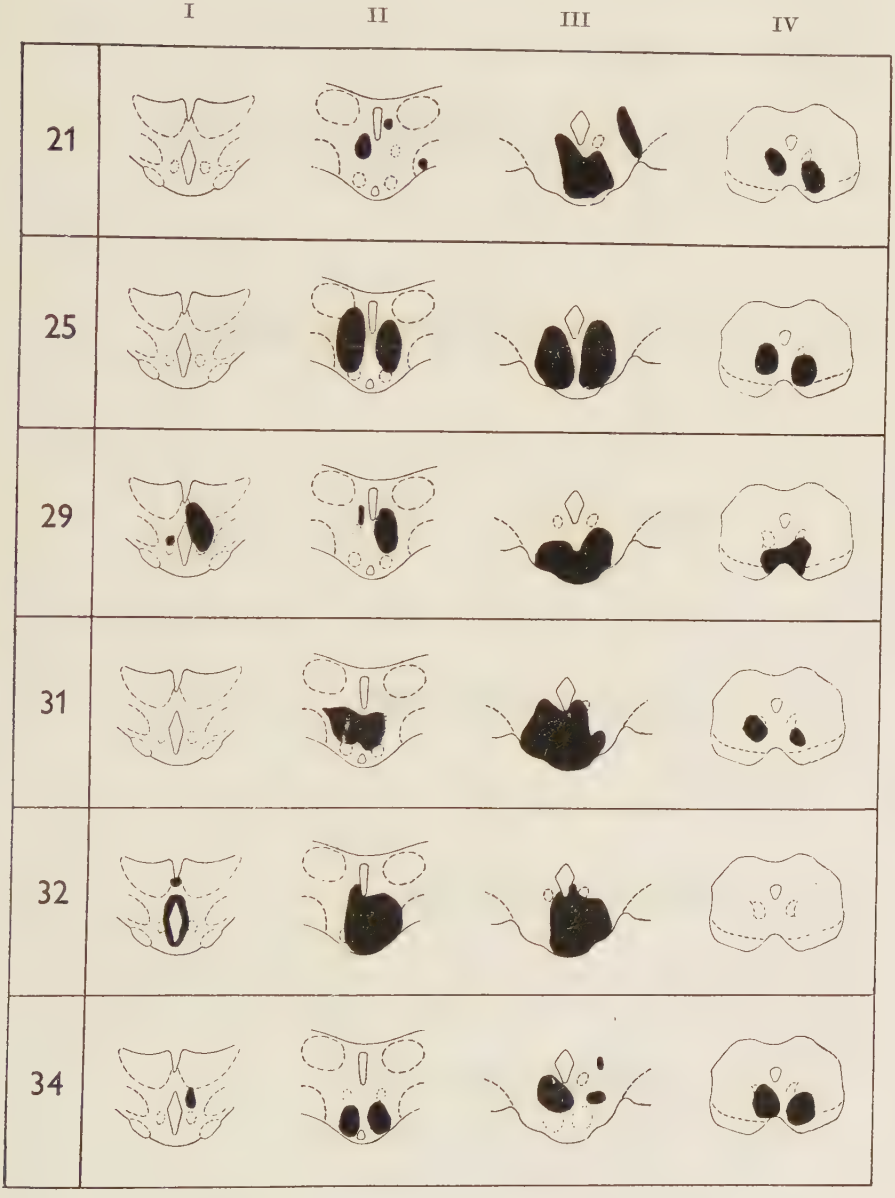
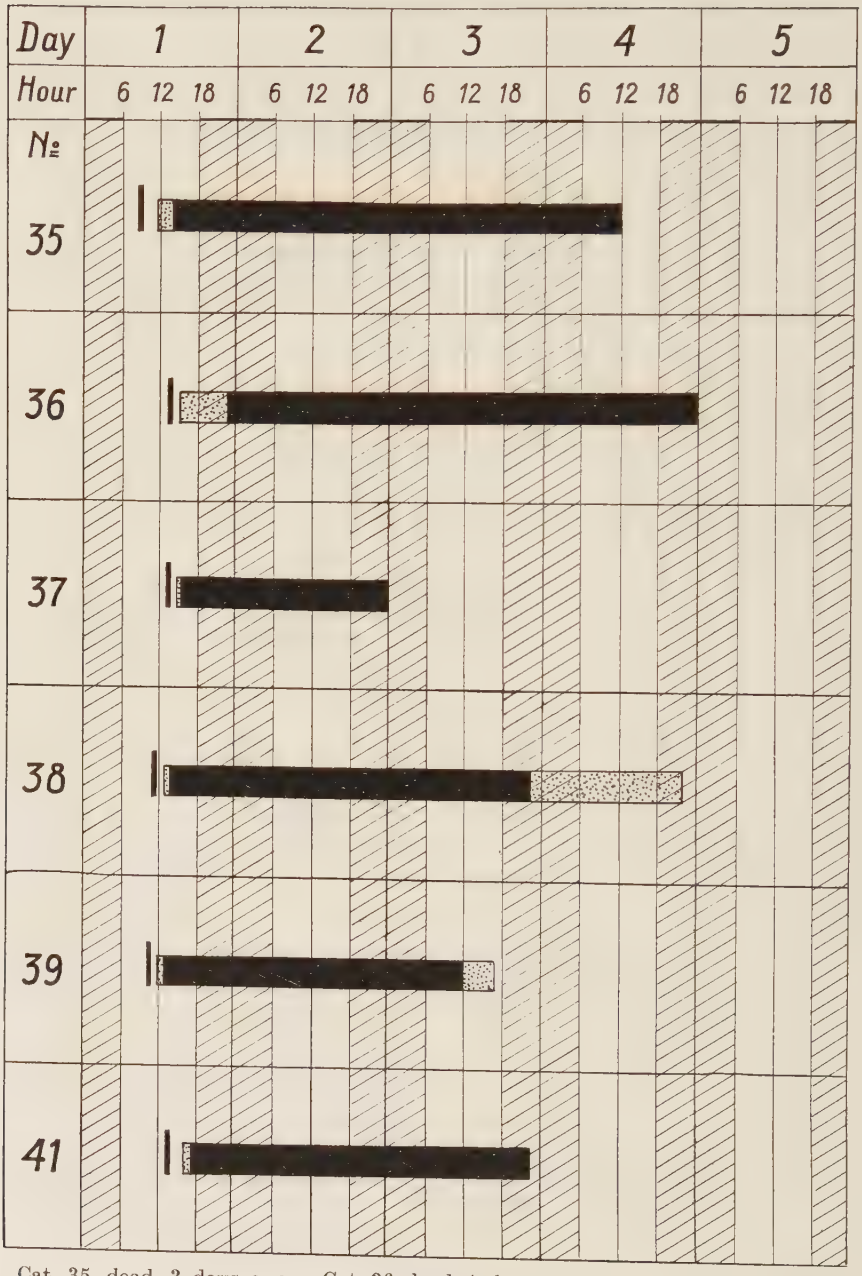
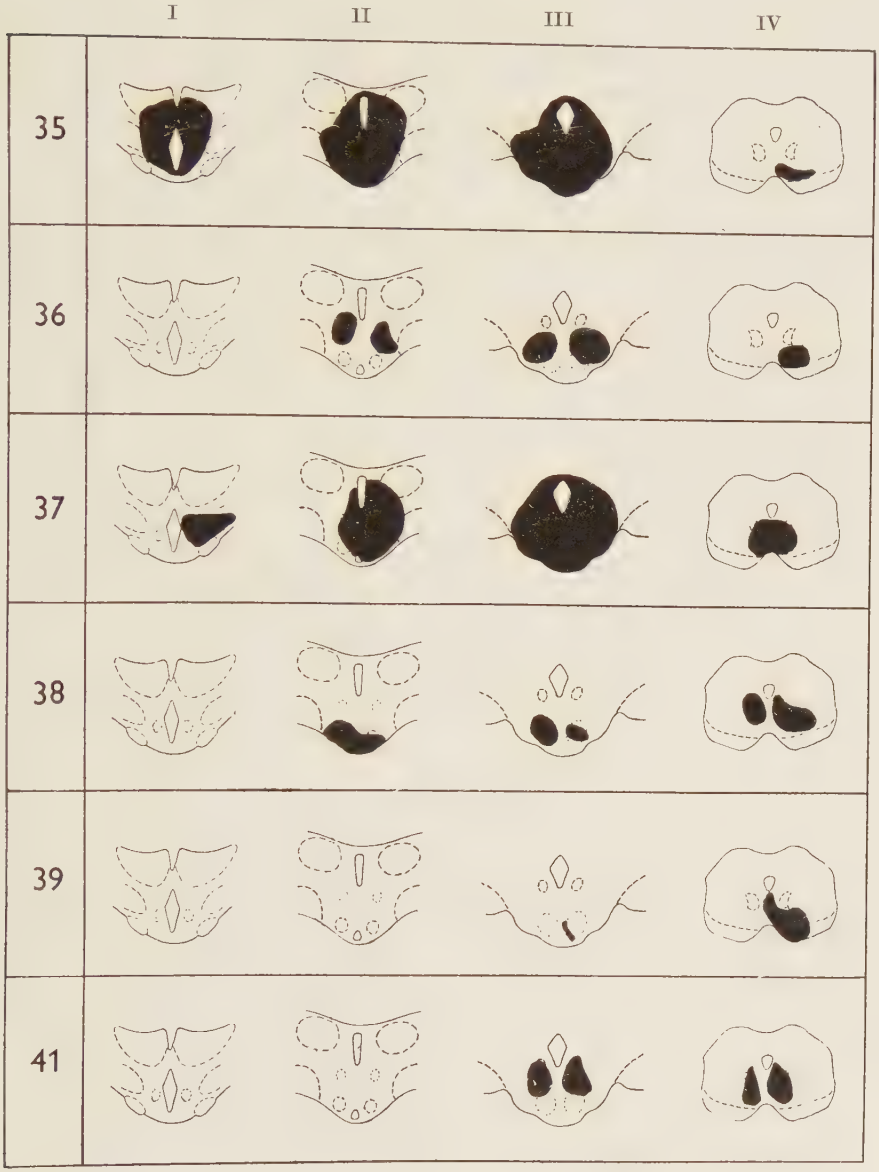


TABLE II (cont.).



Cat 35 dead 3 days a. op. Cat 36 dead 4 days a. op. Cat 37 dead 1 ½ days a. op. Cat 38 killed 20 days a. op. Cat 39 killed 15 days a. op. Cat 41 killed 1.5 months a. op.

I. Transverse section through the brain stem at the boundary between the anterior and posterior parts of the hypothalamus. II. Section through the anterior part of the corpora mamillaria. III. Section through the corpora mamillaria. IV. Section through the anterior part of the mesencephalon.



In a few experiments unilateral electrolysis was performed on one day without any sleep effect. The day after electrolysis was made on the other side and the usual sleep period was induced.

In not a few experiments the animal died a number of days after the operation (cf foot notes respecting Table II). In one case the autopsy revealed bronchopneumonias, but in the other cases there were no patho-anatomical changes excepting the hypothalamic injury which occasionally was not particularly extensive. In those cases the cause of death was obscure.

It would be of considerable interest to ascertain how the operated animals behave in respect to the sleep-wakefulness rhythm after the acute sleep effect has terminated. Such an investigation is rendered difficult however because a normal cat, kept prisoner in a cage, lies still in a corner the greater part of the day and practically only moves about during the short intervals in connection with the taking of food and for other natural functions. It is therefore very difficult to obtain an idea of the normal animal's sleep-rhythm in enforced captivity. It should perhaps be mentioned that the cat material almost exclusively consisted of stray cats. The solitary tame cats placed at the authors disposal for the investigation have behaved in quite another manner. They generally get up and go backwards and forwards in the cage as soon as anyone enters the room and continue with the same as long as the person in question is within sight or earshot. As a rule, however, the operated animals have been more active than those not operated (the stray cats), which might possibly indicate that the operation had produced hyposomnia. This observation has of course little demonstrative value in this respect because it for the present has the character of subjective judgement.

Summing up the matter it can accordingly be said that the above experiments have disclosed that the bilateral tissue destruction by electrolysis within the posterior part of the hypothalamus of cats involves a sleep effect of some days' duration which agrees well with what earlier has been described in literature. One essential observation is however, that this sleep period does not set in immediately after the operation, but after an interval of some hours. An important, negative find is, that the sleep effect could not be produced after such operations within the hypothalamus of rabbits.

3. The mechanism of the sleep effect.

The interpretation of these results, and of those in previous surveys of experiments involving the hypothalamic region, offers great difficulties. In discussing and interpreting the experimental results one must start from two diametrically opposite premises: either the hypothalamic regulating centre is a *wakefulness centre* or it is a *sleep centre*. In the following the separate observations will be examined from both these two points of view.

Ranson and co-workers are of the opinion, as already mentioned, that their observation that sleep ensues after the destruction of tissue within the hypothalamus (cf p. 22) is a direct proof that the regulation centre situated here is a *wakefulness centre*. This interpretation implies that the effect of the operation is to inactivate a nervous centre whose intact function is necessary to keep the individual awake. This does not explain however why the animal wakens up a few days after the operation. The literature on the whole contains no satisfactory discussion on this fact. A theoretical explanation here may be that the parts of the centre which were not destroyed by the operation should have recovered enough functional capacity after these few days for a compensatory over-function, sufficient to keep the individual awake. Such a mechanism however would imply an extraordinary manner of reaction on the part of the nervous system. As a rule, it takes a long time before compensatory functions become active in cases where such functions develop at all, and this by reason of the central nervous system's slight capacity for regeneration.

The observation of a sleep-free interval after the operation within the hypothalamus apparently complicates the problem still further. If the centre is a wakefulness centre, this interval can be interpreted in two different ways, both of which presume that the regulation centre was not totally destroyed at the operation. Firstly, one might assume that the remaining intact parts of the centre are able through over-function, to keep the individual awake for a short period, but that they soon become exhausted and the animal falls asleep. But even such an early compensatory over-function would be an extraordinary condition within the nervous system. The other possibility would be that the toxic effects of the necrosis would depress the function of the remaining parts of the centre, but that such an effect

could not attain a sufficient intensity before some time had elapsed after the operation. However, if this explanation be correct, one would expect sleep effect even with necroses located in the nearest surroundings of the hypothalamus. According to reports in the literature, and to the author's own experience, such is not the case. In this connection should also be pointed out that in some tests a very extensive tissue injury was brought about within the hypothalamus as well as within the adjacent parts of the brain stem and the animals exhibited a sleep-free interval after the operation, all the same. This circumstance renders hardly probable the interpretations which postulates a partial destruction of the regulating centre, to such an extent, that parts, sufficient for the function, still remain.

In order to bring HESS' observations (cf p. 21) into accord with the postulate, *wakefulness centre*, it must be assumed that the sleep effect of the weak, pulsating direct current — contrary to HESS' own opinion — was due to inhibition and not to stimulation of the hypothalamic function. On the other hand, the opinion of RANSON and HARRISON (1940) that the sleep effect in HESS' tests was due to necrosis of the tissue, can scarcely be correct. If such had been the case, the animals should logically have slept as long a time as in RANSON's own experiments, but the animal slept on the whole only as long as the current was acting. Moreover, one and the same animal could be induced to sleep in several spells although the electrodes, due to their fixation, affected the same parts of the brain each time. HESS had finally chosen the pulsating direct current because he was of the opinion that in other tests he had proved it to have a stimulating effect on other parts of the nervous system. In their attempts to reproduce HESS' experimental results, RANSON and HARRISON observed states of irritation ("sham rage") instead of sleep. This may possibly have been due to differences in strength and type of the current.[1]

[1] The question can be asked here also as to whether it is right to regard a state of irritation as a potentiation of wakefulness. In conditions of irritation and agitation probably even other parts of the brain are involved in a manner which has nothing to do with the physiological sleep-wakefulness rhythm. It is known moreover that during otherwise normal sleep, a fairly considerable, both psychic and physical agitation can become manifest, as well as signs revealing activity of the sympathetic part of the autonomic nervous system. Obviously there is no total inhibition of sympathetic activity during normal sleep.

As earlier put forward (p. 18), it has been observed that simple operative intervention with an instrument of fine calibre within the hypothalamus region can produce sleep. With the given premise, *wakefulness centre*, this interference would thus imply an inhibition of the function in the centre in question. It would seem improbable that the sleep effect should be due to tissue damage. It is true that such an injury has been caused at the place of intervention, and perhaps also to the nearest surroundings on account of the great vulnerability of the cerebral tissue. If the sleep effect is produced by this relatively diminutive injury, then the achievement of effect should only be attainable after intervention within a very limited area, where a great part of the centre could be destroyed at one time, but this is not the fact. It should also be pointed out that the interpretation of the effect of a simple intervention within the hypothalamus as being the result of depression of the function is, to some extent, at variance with the experience of similar operations within other parts of the nervous system, which generally call forth symptoms which may reasonably be assumed to be stimulation phenomena.

From the above discussion is revealed that in interpreting the experimental results one must have recourse to less probable arguments in order to bring the individual facts into accordance with the given premise, i. e. that the regulation centre is a wakefulness centre. However this theory in respect to the manner of the function of the centre cannot be looked upon as rejected with absolute certainty.

If, on the other hand, the hypothalamic regulation centre is assumed to be a *sleep centre,* then HESS' interpretation of his experimental results must be accepted and, moreover, the sleep effect of a simple intervention must be the result of stimulation. Here however one is faced with the apparently paradoxical fact that both injury to and stimulation of one and the same part of the brain produce the same effect.

In the attempts made to interpret the mechanism of the sleep effect due to tissue destruction through electrolysis within a supposed hypothalamic *sleep centre,* here must be recognised that there is a secondary influence from the necroses on the parts of the brain assumed to be the effector organs of the hypothalamus in the sleep regulation. As earlier stated (p. 24), it is especially the thalamus but also the vegetative centres in the brain stem and parts of the extra-

pyramidal system which are presumed to be under the influence of the hypothalamus in the determination of sleep. With respect to the thalamus, it would seem that a justifiable assumption is, that an inhibition of its function contributes the loss of consciousness of the surroundings during sleep. The effect of hypothalamic necroses on surrounding parts of the brain may, theoretically viewed, be of a neural or humoral nature. A purely mechanic effect seems highly improbable by reason of the small size of the necroses in comparison with the effector organs.

A *neural* mechanism seems however almost out of the question. A necrotization of a nervous centre must involve an instantaneous cessation of its function. Impulses leading to an active inhibition of, for instance, the thalamic function could of course not issue from a destroyed hypothalamic sleep centre. With regard to the assumption of a partial destruction and a substituting function of centre-remnants, the same arguments can be raised as earlier in the discussion respecting whether the regulation centre is a wakefulness centre or not. It would seem difficult on the whole plausibly to interpret the three phase course (wakefulness—sleep—wakefulness) following hypothalamic electrolytic lesions as the result of a purely neural mechanism.

The possibility then remains of a *humoral* effect from the necroses on the surrounding parts of the brain. It must be assumed in the first place that from the necroses toxic substances are released, which are transferred to the effector organs of the hypothalamus, where they affect the function in such a way, that sleep ensues. Such an assumed resorption of sleep-inducing substances is, in that case, decidedly not the same as the resorbtion of the necroses in its entirety, which requires a long time (months), while the sleep effect only lasts some few days.

As previously mentioned, it is only necroses within the limited posterior hypothalamic region that produce sleep effect, and not similar lesions in the immediate neighbourhood of this region. This would seem to argue that necroses within the posterior hypothalamic region contain *specific sleep-inducing substances* whose action on the hypothalamic effect organs coincides on the whole with the physiological influences from the centre for sleep regulation which causes sleep.

The question then arises as to the manner in which the assumed substances reach the effector organs, that is to say, chiefly the surrounding brain centres.

Transport via the blood vessels is theoretically possible. Such transport would take place similarly to that of the products of the endocrine organs, in other words, the active substances from the places of formation would be secreted into the blood and distributed throughout the whole of the blood to then reach and act upon the various effector organs. In conformity with the hormones the transported hypothetical products of necroses from the hypothalamus, in this way, have effect in very small doses and in low concentrations. The experiments of NERI *et al.* (1934) partly argue against this possibility of transport of the postulated sleep-inducing substances. Between two dogs these authors established a cross-circulation. One of the dogs was induced to sleep by means of hypothalamic puncture, but the other dog failed to show any tendency to sleep. But, as KLEITMAN has pointed out, NERI's *et al.* results are no definite proof against a humoral mechanism.

When the majority of the centres which are assumed to be under hypothalamic influences in the sleep regulation are in close topographic relation to the hypothalamus, there appears to be the possibility that the postulated sleep-inducing substances are transported to the effect organs direct through the brain tissue from the necroses to the surrounding centres. If such be the case, a similar transport could take place via the perivascular spaces of *Virchov-Robin* or perhaps even direct through the cerebral parenchyma. CUSHING (1925) and his school are of the opinion that still finer tissue channels terminate in the said perivascular spaces, which in their turn are in communication with the fluid spaces in the loose network which the entire brain tissue can be said to comprise. That a transport of tissue fluids occurs in these channels can be looked upon as proved by the investigations of WEED and others (cf CUSHING). As support for this opinion one can call to mind the observation from human pathology that degenerative products from centrally situated encephalomalacias can be met with at relatively long distances from the place of formation. A parallel can be drawn also in respect of such transport of postulated products of necroses with the transference of endocrine active substances. Transport of hypophysial hormones from the hypophysis via the stalk to the

hypothalamus has been demonstrated. These investigations will however be referred to in Chapter IV.

The assumption of a humoral mechanism for the sleep effect brought about by tissue destruction within the posterior hypothalamus affords an apparently plausible explanation of the three-phase course of the effect. Whichever of the above mentioned ways of transport the postulated substances can be assumed to choose, a certain amount of time must be required before the concentration within the effect organs has attained a sufficiently high level to produce sleep effect. This might be the cause of the sleep-free interval. When, moreover, the supply of the substances in question is exhausted, the animal again wakes up.

In the literature there is a report which is of interest in this connection. Bizzart *et al.* (1939) have shown that the immediate effect of tissue destruction within the anterior part of the hypothalamus of dogs is diabetes insipidus which however only remains during the first day after the operation. Throughout the following week or so, the excretion of urine keeps at a normal level, but later, during a period of a few days, a lasting diabetes insipidus develops. This three phase course is thus similar to the effect on the sleep regulation after electrolytic lesions within the posterior hypothalamic region. Both the effect on diuresis and the sleep effect may receive a plausible theoretical interpretation on the assumption that the pre-formed substances which inhibit diuresis and induce sleep are resorbed from the necrotic tissue. The diabetes-free period, which consequently corresponds to the sleep period, would thus be due to the exhaustion of the depôt of specific substances, which the necroses are supposed to constitute. The observations of Bizzart *et al.* reveal that an influence on the humorally regulated water metabolism has in principle the same course as a similar influence on the sleep function for which the possibility of a humoral mechanism has been assumed.

Starting with the premise that the hypothalamic regulation centre is a *sleep centre,* a theoretical explanation can be achieved of all the results obtained in that part of the experimental sleep research which involved operations of various kinds within the hypothalamic region. In respect to the interpretation of the effect of tissue destruction within the centre, it must then be anticipated, as already assumed probable, that substances are released from the necroses which affect the effector organs of the hypothalamus in the regulation of sleep.

The fact to which attention is called in the literature and which the author's investigations partly support that the electrolysis must be performed bilaterally can hardly be used as an argument in the discussion as to whether the sleep effect is due to a neural or a humoral mechanism. It only seems to indicate that the effector organs of the hypothalamic regulation centre must be bilaterally influenced in order to produce sleep effect.

The conditions respecting the regulation of sleep after the termination of the acute effect of the tissue destruction within the hypothalamus are evidently dependent upon the extent to which the regulation centre has been destroyed. The sleep regulation will either be severely disturbed or the remaining parts of the centre will be able to maintain a more or less good sleep regulation. Should the centre be a wakefulness centre, the latter alternative would seem always applicable, as, judging from the literature as well as from the present results, a chronic state of sleep is never observed after electrolysis within the hypothalamus, although at times a very extensive injury to the tissue is brought about. If on the other hand, the centre is a sleep centre, one might expect the experimental animal sometimes to manifest an incapacity to sleep. No such condition has been reported in the literature. The present observation that the animals, in the period following the acute effect, are apparently more active in the cage than is the normal animal, may perhaps indicate hyposomnia. Even if the said observation lacks the value of an objective demonstration, the conditions in the later period after electrolysis within the regulation centre must be said to argue more in favour of a *sleep centre* than for the contrary.

The same conclusion can be arrived at by analysing the clinical symptoms regarding the sleep disturbances in acute and chronic encephalitis against the background of the patho-anatomical changes. The conditions in respect of encephalitis lethargica may be said, in some measure, to constitute a parallel to the effect of hypothalamic electrolytic lesions. The acute encephalitic somnolence and sleep can be explained *à priori* as being due to the inflammation causing either stimulation or depression of the function within the regulation centre. The hyposomnia which is a common symptom in chronic encephalitis, can scarcely be regarded otherwise than as a symptom of degeneration on account of the histo-pathological picture with ofttimes extensive disappearance of the specific tissue, i. e. the nerve

cells. From this follows that of the two alternative interpretations of the somnolence and sleep in the acute stage, only the first can be applicable. The most natural interpretation of the sleep disturbances in encephalitis is therefore as follows: [acute inflammation—stimulation—sleep] and [chronic inflammation—diminished function—hyposomnia]. The conclusion of this argument is accordingly that the regulation centre should be regarded as a *sleep centre.*

In this discussion attention should be drawn to the fact that it seems impossible to produce sleep by means of electrolysis within the hypothalamus of rabbits, as seen from the present results. The almost complete lack of information in the literature on the sleep problem with reference to experimental interventions within the hypothalamus of rabbits, is probably owing to similar negative experiences which have not been published. The phenomenon seems to have been discussed only once in the literature, and this was when Spiegel & Inaba (1927) incidentally stated that "Tiere mit höher differenziertem Cortex für solche Versuche besser geeignet scheinen als das lissencephale Kaninchen." Such a statement however affords no satisfactory explanation of the non-appearance of the sleep effect.

The rabbit's polyphasic diurnal rhythm might be taken into consideration while discussing this problem. The difference between the mono- and polyphasic sleep-rhythms can of course be determined as due to dissimilarities in the rhythm of activity of the hypothalamic regulation centre. It is known however, and principally through Forsgren's, Möllerström's and Holmgrens's works on the rhythmic functions of the organism (cf Möllerström 1943), that animals with a pronounced polyphasic sleep-cycle, such as rabbits, with regard, for instance, to the glykogen metabolism of the liver, display a monophasic diurnal rhythm. The monophasic rhythmic changes of the function of the liver and other organs are dependent on a similar rhythm within the activity of the vegetative-endocrine system. The discrepancies between the monophasic rhythm of these functions and the polyphasic sleep rhythm in these animals is therefore striking. By reason of the fact that the various vegetative and endocrine functions are so intimately combined and affected by each other, it would seem improbable that one of these functions should have a rhythm so fundamentally different from all the others. An observation worthy of notice in this connection is that barbiturates

do not appear to have a hypnotic effect on the rabbit. In the experiments referred to in Chapter III, it was proved that 1 cg barbiturate had no outwardly perceptible effect on the rabbit while cats usually became exceedingly somnolent after a corresponding dose. No noticeable disturbance of the consciousness of rabbits occurs exept with doses producing narcotic effect. It must be confessed however that the criteria respecting a rabbit's sleep are vague. For these reasons it might be assumed that animals which have a polyphasic diurnal rhythm for their activity are devoid of a real sleep function. This means that those numerous inactivity periods taking place during the twenty-four hours, and which were earlier called sleep, are not sleep in the same meaning as, for instance, that of human beings and cats. These periods of inactivity would not involve the same profound mental and vegetative readjustment, with the incidental functional change in a number of organs and systems, as among individuals with a monophasic diurnal rhythm for sleep-wakefulness. The rabbit would thus be lacking in a sleep regulation centre within the hypothalamus, and consequently also be incapable of reacting with sleep to various interventions within this part of the brain.

This observation concerning the apparent incapacity of the rabbit to react with sleep after the destruction of tissue within the hypothalamus can be employed as argument in the discussion of the problem: wakefulness or sleep centre? If the regulation centre is assumed to be a wakefulness centre in the cat, there should reasonably be a similar centre in the rabbit too. If the rabbit can be presumed deficient in sleep function it cannot be pronounced destitute of the capacity to be awake. Should the rabbit accordingly possess a wakefulness centre within the hypothalamus it would, in that case, react with loss of the state of wakefulness, i. e. with sleep or some other disturbance of consciousness, subsequent to tissue destruction within such a centre. A better explanation of the missing sleep effect can be obtained however if the assumption is made that the rabbit's above postulated lack of sleep function corresponds to the absence of a *sleep centre* within the hypothalamus.

* * *

The discussion of the acute, three-phasic effect on the regulation of sleep-wakefulness after tissue destruction within the posterior part of the hypothalamus of the cat has yielded the result that an interpretation of the observations is possible if based upon both the diametrically opposite premises: wakefulness and sleep centre. The conditions following the termination of the acute effect as well as the missing sleep effect of similar operations on the rabbit, have however rendered it probable that *the hypothalamic centre for sleep regulation is a sleep centre.* The conditions in respect to encephalitis lethargica point in the same direction.

CHAPTER III.

The sleep function elucidated by interpreting the hypothalamic regulation centre as a sleep centre.

The previous chapter led to the conclusion that the centre for sleep regulation within the posterior part of the hypothalamus should be regarded as a sleep centre. For such an assumption to be justifiable it should be found in logical accordance with our present knowledge of the physiology, pathology and pharmacology of the sleep function, likewise also with the results of experimental sleep research.

1. The physiology of sleep.

Within the hypothalamic region there are a number of centres regulating vegetative-endocrine functions. Most of these functions, if not all, are changed in some way during physiological sleep. In his extensive monograph KLEITMAN has exhaustively treated these, as he according to PIÉRON calls them, "concomitants of sleep." In the following however only a few details will be touched upon.

It has long been known that influence exerted in one way or another on the vegetative-endocrine functions can either promote or prevent sleep. Many of the instructions which have been given for the relief of sleeplessness are just attempts to change these functions by various means in the same way as they are changed during physiological sleep (for instance, by obtaining a basic state of the pulse, blood-pressure and respiration, changes of bodily temperature and muscular tone, decrease of blood-sugar). The mechanism of the sleep effect of such measures must in many cases be presumed to involve the hypothalamic regulation centres. The reciprocal influences of these centres might reasonably be thought to occur in

such a manner that either increase or decrease of the activity within one of them produces a corresponding change within the other adjacent centres. If such an assumption be correct it would be possible, taking some known hypothalamic function as a basis, to find out in what manner the hypothalamic centres affect other functions. It would seem suitable to start with water metabolism. It must be highly probable that an adequate hypothalamic (and neurohypophysial) function is one of the conditions of a good water balance and moreover, that injuries within this region can bring about diabetes insipidus among other disturbances. Furthermore when it is known that the excretion of urine is diminished during sleep, the conclusion may be drawn that both sleep and the decrease of diuresis during sleep are dependent upon *increased* hypothalamic activity. This argument leads back to the conclusion that the centre for sleep regulation within the hypothalamus is a *sleep-centre*.

In this connection attention should be drawn to the fact that the so-called "concomitants of sleep" are not absolutely necessary accompaniments of sleep. The main characteristic of sleep, the condition of unconsciousness of the surroundings which is reversible through waking, is thus not unconditionally dependent upon complete parasympathotonia. It is known, for instance, that sympathotonic reactions may be observed during sleep. Another example of dissociation between loss of consciousness and other accompaniments of sleep is somnambulism both in its ordinary sense and in form of the well-known phenomenon that soldiers are able to sleep while on the march.

The physiological monophasic diurnal rhythm for sleep-wakefulness in man thus reproduces alternations in the activity within the hypothalamic centre. How these changes come about is however still unknown. From the introductory survey of the literature it is gathered that certain facts argue that the centre possesses at least some degree of autonomy (p. 19). Influences from other organs obviously play a more or less prominent rôle here as well as in regard to the other vegetative functions. Even if the centre for sleep regulation can thus be assumed to have a certain degree of autonomy in its functional cycle, it is nevertheless readly influenced by both psychic and sensory as well as vegetative-endocrine and chemic-toxic agents. But how much such factors play a part in normal sleep rhythm is impossible to say as matters stand today.

2. The pathology of sleep.

The individual variations in the duration and depth of sleep should reflect differences in the functional cycle and intensity of the hypothalamic centre. The differences can be of a primary or secondary nature, that is to say, they can be caused by variations in the function of the centre itself or by dissimilarities respecting the quantity or type of influences from other organs and centres. The demarcation between what may be considered physiological and pathological is not clear.

The most usual disturbance in respect of the regulation of sleep is hyposomnia (insomnia, agrypnia). This symptom is particularly common in the so-called vegetative neuroses, in other words, conditions which occur with, sometimes, frequent disturbances which might be caused by functional disturbances within the vegetative centres. Such states can of course be due to a primary disturbance within these centres, but in many cases one has reason to believe that it is a question of secondary influences on the centres, and primarily those of endocrine nature. Thus hyposomnia should be due to a primary or secondary defective function of the sleep-centre. Nothing argues against such an assumption even if these experiences provide no direct support for the view that the centre is a sleep- and not a wakefulness centre.

The position in regard to encephalitis lethargica and its sequelae has been discussed earlier (p. 49).

Sleep disturbances in narcolepsy offer some interesting details. The definition of the syndrome of narcolepsy is so vague, and the symptoms included under this diagnosis are so various that it is difficult to interpret the patho-physiology of this condition unitarily. Undoubtedly a number of narcolepsy cases should be included under the diagnosis epilepsy (petit mal, epileptic absences) and accordingly the attacks of unconsciousness have nothing to do with sleep regulation in its proper sense. The discussion here will be accordingly limited to cases where the symptoms can presumably be caused by disturbances in the physiological sleep rhythm. These cases may be classified on the whole into three groups.

To the first of these groups belong those cases of narcolepsy which, between the sleep attacks, manifest chronic and continous readiness

to sleep. Here the reason might presumably be chronic irritation with hyperfunction of the sleep centre.

The second group should be the one in which the sleep attacks set in more gradually and in the individual case in connection with some often determined stimulus (for instance, after meals). The sleep attacks in these cases might be due to temporary increase of activity in the sleep centre brought about by such stimuli.

The third group, fundamentally distinct from the two previous ones, is comprised of those narcolepsy cases in which there occurs considerable disturbance of the night sleep, i. e. cases, which according to THIELE & BERNHARDT, display a tendency towards transition from the monophasic to polyphasic diurnal rhythm (cf p. 17). The assumption is not impossible that the sleep centre in these cases may be considerably injured or in a condition of chronic hypoactivity. This would involve a pronounced hyposomnia which in its turn would deprive the central nervous system of the, no doubt, necessary rest from exogenous impulses. Thus the attacks of unconsciousness in these cases would not be viewed as sleep attacks but maybe more plausibly as refractory periods for exogenous impulses. In respect to this interpretation of the mechanism of narcolepsy, it would not seem out of the way to draw a parallel with the rabbit's inactivity periods which are not considered to be sleep in the ordinary sense (cf p. 50).

3. The pharmacology of sleep.

The barbiturates occupy a special position among the hypnotics due to the fact that the somnolence and sleep they induce, are very similar to the corresponding physiological conditions. Although these barbiturates are one of the groups of drugs which has been most frequently employed in clinical practice for nearly half a century, and in spite of intensive pharmacological research, their mode of action is still for the most part unclear. It has generally been thought that the barbiturates have a depressant effect on the functions of the central nervous system. It is obvious however that all drugs which can be used as general anesthetics, and the barbiturates belong to this category, have not the same amount of effect on all parts of the nervous system. PICK (1928) has divided hypnotic drugs into

two main groups. There are those which chiefly act upon the cortex (ether, paraldehyde, chloral, bromides etc.), and those which have their principal seat of action within the brain stem (mainly the barbiturates). Pick accordingly talks about "cortical and brain stem hypnotics." The observations on which this division is based are, broadly speaking, the following. In animal tests the barbiturates have been found in greater concentrations within the brain stem than within other parts of the brain (Pick 1928, Keeser & Keeser 1927 etc.), while other narcotics have been found to be evenly distributed within the central nervous system. Leiter & Grinker (1934) have shown that the vasomotor and respiratory effects obtained by hypothalamic stimulation disappear earlier under the influence of anesthesia with barbiturate derivative (dial) than with ether. Furthermore, the earlier mentioned tests (p. 23) with comparative temperature measurements within the brain stem and cortex were interpreted as the result of a more intensive depression of the function within the brain stem than elsewhere under the effect of barbital (Feitelberg *et al.* 1939). The above mentioned fact that the barbiturates induce a physiological sleep with the whole of the typical vegetative readjustment is the first of the clinical observations which have been taken as support for Pick's classification. The electroencephalogram is also of the same type in both physiological and barbiturate-induced sleep as distinct from sleep brought about by "cortical" hypnotics (Bremer 1937, Davis *et al.* 1938, Gibbs 1945). Moreover, the barbiturates have been found to be more or less ineffective as hypnotics in postencephalitic conditions, and they are liable to render the tremor worse in Parkinsonism (Ziskind & Ziskind 1937). The effect of barbiturates is thus changed in conditions where there is localized injury within the brain stem.

However, a number of objections have been raised to the above division of narcotics into "cortical and brain stem drugs." Koppany *et al.* (1934) consider they have demonstrated, in contradiction to Pick and Keeser & Keeser, that the distribution of barbiturates within the brain is as uniform as that of other narcotics. As is also put forward in the literature, an accumulation of barbiturate in the brain stem is no conclusive proof of a specific seat of action within this region. The selective tissue injury within the juxtaventricular parts of the brain stem with chronic barbiturate administration (Seevers & Tatum 1931, van der Horst 1934, Incze 1935) may

only be the result of greater sensitivity within the juxtaventricular grey matter of the brain stem (or due to higher concentration), and not a sign that the drugs are specially active there.

In his monograph KLEITMAN summarizes his impressions gained from the literature respecting the pharmacology of sleep by saying that it would seem probable that different narcotics have dissimilar mechanisms of action on the central nervous system, but that it is not certain, for instance, that all the barbiturate derivatives are to be classified as "subcortical drugs." GOODMAN & GILMAN (1941) are apparently of the same opinion, as they state that "it cannot be denied that the barbiturates may selectively depress certain functions mediated by subcortical centers."

When it has been asserted that the barbiturates have a special seat of action in the brain stem, it has been simultaneously assumed that reference was being made to a *depressant* effect. But how then does this opinion coincide with the interpretation that the hypothalamic centre for sleep regulation is a *sleep centre?* If the barbiturates have a particular effect on a centre whose increased activity induces sleep, the effect should reasonably be one of *stimulation* and not of depression. AGERBERG (1941) earlier reached the same conclusion. Can then the assumption of a stimulating effect by the barbiturates on the sleep centre be justified? It may perhaps be thought that a stimulating effect by a narcotic would be a contradiction in terms. It is however no unusual phenomenon that pharmacologically active substances have quite contrary effects on different parts of the organism and, further, that substances which, in low concentrations produce a stimulating effect, act depressively on the same function when administrated in higher dosage. Theoretically there is thus the possibility that the barbiturates stimulate the hypothalamic functions while depressing the functions of other parts of the brain, primarily those centres in which inhibition would involve sedation and anesthesia. There is also the possibility of the barbiturates stimulating the hypothalamic functions in low concentrations, and inhibiting in increased dosage. In this connection it should be pointed out that by the indication "brain stem" or "subcortical drugs" it is not necessarily meant that the barbiturates produce the same degree or kind of effect on all parts of the brain stem.

A few examples of results of pharmacological experiments might

be brought forward in this connection. They have been regarded as an indication of a stimulating effect induced by the barbiturates. Burnstein & Rovenstine (1938) have published that some barbiturates bring about adduction of the vocal chords, an effect which can be prevented by atropine. These authors are of the opinion that this parasympathetically mediated reflex is stimulated by the barbiturates. Further, Gruber *et al.* (1938) have demonstrated that certain barbiturates, at least in moderate dosage, bring about a sensitization of the vagus to electric stimulation.

Important clinical observations have been published in the literature. These are often referred to but seldom discussed. They can be regarded as support for the assumption that the barbiturates have a stimulating effect in hypnotic dosage on the hypothalamic sleep centre. Such a stimulation may be *direct* or *indirect*. Either the barbiturate can stimulate the sleep centre directly, or the augmentation of function can be caused by the barbiturates diminishing the inhibitory effect of other brain centres on the hypothalamus which latter remains uninfluenced by these drugs in hypnotic dosage.

One of these clinical observations is, that hyposomnia in the postencephalitic state, where, among other parts of the brain stem, the hypothalamic region is the site of injuries in the form of nerve cell degeneration, is very little affected by or quite resistant to barbiturate (cf Goodman & Gilman). It seems difficult to reconcile this circumstance with the assumption that these drugs have a depressant effect on the hypothalamus. In such a case the same dose, or perhaps a lesser one, should be necessary in order to obtain the same effect as under physiological conditions. The increased resistance is more easily explained on the assumption that the barbiturates have a stimulating effect on the hypothalamus. If this be so, it can be assumed that a greater dosage, that is to say, a stronger stimulation, would be required to achieve the same total effect which a smaller dose has on an uninjured organ of normal size.

The second clinical observation which can be regarded as support for the assumption of a stimulating effect by barbiturates on the hypothalamus, is the "paradoxical" effect these drugs may have in postencephalitic conditions and also sometimes among what appear to be healthy individuals, especially when the external circumstances

render it difficult or impossible to sleep after the drug has been administered (for instance where is much exogenous stimulation or pain). This paradoxical effect manifests itself by the individual becoming wide awake, excited and quite incapable of sleep after the administration of a normal or greater dosage. If the barbiturates produced an inhibitory effect, an increased dosage would be expected to bring about an increase in inhibition. Instead, when the paradoxical effect occurs, an initial tendency towards sleep passes over to excitement. Of course, increased dosage in these cases can cause disturbance of the consciousness, but the effect will then be narcosis and not sleep.

From the literature concerning the pharmacology of the barbiturates (monographs: Tatum 1939 and Goodman & Gilman 1941) it is seen that comparatively little interest has been devoted to the effect of these drugs in *hypnotic* dosage. The majority of investigations have been made with dosage and concentrations corresponding to *narcotic* effect, and yet it is undoubtedly of great importance to distinguish between these two effects. The sleep effect should be looked upon as the inducement of a physiological condition and, as earlier pointed out, there are a number of observations which indicate that it is the result of an influence on the hypothalamic regulation centre for sleep. Narcosis, on the other hand, is an exceedingly pathological condition, which is presumably caused by an inhibition of the function of several brain centres. Narcosis, for this reason, may perhaps be better considered as a continuation and intensification of a sedative effect, than as a potentiation of sleep.

According to the above assumption the normal central effect of the barbiturates is comprised of two different components. The first is a depressant one, increasing with increasing dosage, and affecting those centres whose inhibition leads to sedation and narcosis. The other component should be a direct or indirect (see above) stimulation of the hypothalamic sleep centre (and maybe also of the other hypothalamic, vegetative regulation centres), which stimulation should induce sleep. With increasing dosage the stimulation would change into depression whereupon sleep would merge into narcosis because of the pronounced inhibition of the function of other parts of the brain produced by such doses.

In conditions where the sleep centre is partially destroyed, e. g.

by encephalitic process, the barbiturate stimulation can never be sufficiently intense to produce a sleep effect. The effect of increased dosage on the consciousness will therefore be narcosis without any stage of sleep.

With respect to the paradoxical effect of barbiturates the initial stimulating effect would pass into depression earlier than is normal, with consequent excitation instead of sleep. It is not impossible that, here, inhibiting influences on the hypothalamus from other parts of the brain may be of special significance. As sleep is rendered very difficult or impossible by excess of exogenous stimulation or pain, the conclusion could be drawn that functional activity of the thalamus, which is the collective site of pathways mediating exogenous impulses and pain, implies inhibition of the hypothalamic sleep centre. As stated above, it is just when functional activity of the thalamus may be presumed to be increased that the paradoxical effect of barbiturates can be observed.

With regard to rabbits which are believed to lack sleep function in the same sense as that of man (cf p. 50) the effect of barbiturates on the consciousness would be expected to be restricted to inhibition of the centres in which decreased activity leads to sedation and narcosis.

With the object of experimentally ascertaining the effect of the barbiturates on different parts of the brain, some tests have been preformed to determine the intensity of phosphate metabolism. This has been accomplished with the aid of the radioactive isotope ^{32}P. It should first be stated however that the results obtained allow of no reliable conclusions in either one direction or the other. It is perhaps justifiable to publish the results in this connection as they, in the first place, do not argue directly against the above assumption of a stimulating effect of barbiturates on the hypothalamus, and secondly, they may serve as an example of the difficulty entailed in assessing the results of metabolic tests of this type.

The method employed in these tests has recently been described by Lindberg (1946). In brief, the animal is injected with a certain quantity of ^{32}P in the form of Na_2HPO_4. After a given time, usually 30 or 40 minutes, the animal is killed, preferably decapitated, and the organs or parts of organs in question are excised quickly and analysed with respect to the content of ^{32}P, the number of impulses being calculated in the *Geiger-Müller counter,*

and the total phosphorus content, colorimetrically. The number of impulses per minute divided by the value of the total phosphorus content has been called the *specific activity* of the organ. The relation between the various specific activities within one and the same organism is termed *relative specific activity.* Experience has shown that the specific activity of an organ differs considerably from animal to animal even under as similar experimental conditions as possible, while the relative specific activities generally manifest considerably greater agreement from experiment to experiment. As a rule it can be said that a diminished specific activity indicates a reduced phosphate metabolism which, in its turn, reflects an inhibited carbohydrate (and also fat and protein) metabolism, in other words, it is an expression of inhibition of the function of the organ. An increased specific activity is, on the other hand, not necessarily due to an augmented phosphate metabolism, i. e. by an increase of function, even if such may be the case in the majority of instances. It may also indicate the presence of an accumulation of ^{32}P due to inhibition of one or some of the intermediate stages of metabolism. It is, in fact possible that this occurs in spite of the short experimental interval which was chosen so that the maximal accumulation of ^{32}P in the organs studied was not achieved.

In the author's own tests cats and rabbits were employed as experimental animals. The cats were injected with 0.1—0.15 millicurie ^{32}P intraperitoneally, and they were decapitated 40 minutes later. To the rabbits 0.07—0.1 mC was administered intravenously and they were decapitated 30 minutes after the injection. Half an hour prior to the ^{32}P injection about half the animals were given a mixture of equal parts of *barbital Na* and *phenobarbital Na* (two of the clinically most used barbituric acid derivatives), the cats 2 cg intraperitoneally and the rabbits 1 cg intravenously (1 % solution in H_2O). After decapitation the hypothalamic region was excised in one block and a piece of the thalamus and of the nucleus caudatus was removed from both sides. The relative specific activities *hypothalamus/thalamus* and *hypothalamus/nucleus caudatus* are given in Tables III and IV. Other parts of the brain were also investigated but the dispersion of the values was too great to permit of any inference.

These Tables show that the relative specific activity *hypothalamus/thalamus* is higher under the influence of barbiturate than in the control series. This applies to both cat and rabbit series. A statistic evaluation by the Student's t-test shows that the difference is significant. The relative specific activity *hypothalamus/nucleus*

Table III.

The relative specific activity hypothalamus/thalamus

C = controls
B = barbiturate-treated

Cats		Rabbits	
C	B	C	B
3,89	4,61	1,26	3,07
2,16	4,69	1,98	4,40
2,68	6,38	3,22	3,71
3,35	2,97	1,77	4,60
3,33	5,89	1,76	5,48
2,90	4,48	2,44	3,88
2,45	7,44	1,66	2,28
2,78	6,16	2,76	2,97
2,42	3,17	2,76	4,06
		2,42	2,96
$2,88 \pm 0,18$	$5,09 \pm 0,50$	$2,20 \pm 0,19$	$3,74 \pm 0,30$

Table IV.

The relative specific activity hypothalamus/nucleus caudatus

C = controls
B = barbiturate-treated

Cats		Rabbits	
C	B	C	B
0,86	2,65	0,53	1,05
1,61	2,67	1,42	2,80
1,59	4,13	0,73	1,42
1,48	3,35	0,49	1,48
2,05	1,64	1,04	0,65
1,16	2,77	1,02	0,80
2,50	3,17	0,91	0,78
1,33	2,95	0,99	0,89
			0,91
$1,57 \pm 0,18$	$2,92 \pm 0,24$	$0,89 \pm 0,11$	$1,20 \pm 0,22$

caudatus reveals an increase under the effect of barbiturate, but the difference is significant only in the cat series.

The interpretation of this change in the relation between the accumulation of ^{32}P within the hypothalamus and thalamus entails great difficulties. It is impossible to determine which of the many combinations of increase and decrease of the respective specific activities is the operative one, either from the Tables or from the

protocols on which they are based. Had there existed an organ which remained completely uninfluenced by the barbiturate, this could have been employed as a control organ, and the interpretation would thus have been considerably facilitated, even if there were still difficulties to surmount. From a theoretical point of view none of the interpretations can be said, in itself, to be more plausible than the others. There is thus the possibility that the change of the relative specific activities is partly due to an increase of the specific activity of the hypothalamus and that this increase, in its turn, is due to increased function in this part of the brain under the influence of barbiturate. Such a functional increase however need not in the present case, be the result of a direct drug effect on the hypothalamus. There is also the possibility that it may be due to an indirect effect, i. e. to a diminution of inhibitory influences from the thalamus (and nucleus caudatus?) brought about by the direct drug effect on this centre.

Another possible cause of the changed relative specific activities may be an alteration of the blood content. Laidlaw & Kennard (1940) consider they have demonstrated vascular dilatation within the hypothalamus of monkeys under barbiturate narcosis (under ether narcosis vascular dilatation within the cortex). Gruber *et al.* (1926), in perfusion tests with excised dog brain have achieved vascular dilatation even with small doses of barbiturate. A similar effect is also known to occur in other vascular regions (cf Tatum). Hyperemia with blood having a high ^{32}P content, induced by barbiturate will have a greater effect in the relatively vascular hypothalamus (cf p. 75) than in the poorly vascular thalamus and nucleus caudatus. The above analytic method renders no aid in differentiating between the intra- and extra-vascular ^{32}P. It is true that it might be possible by means of hydrolysis tests and the determination of ^{32}P content of various phosphate-containing intermediate products of metabolism, but the quantity of ^{32}P requisite for such tests is scarcely available in this country at present. If however the demonstrated change of the relative specific activities should be due to hyperemia it is not easy to assess the significance of this for the functional activity of the different parts of the brain. The increased blood flow might of course indicate a purposeful reaction associated with increased function. But the fact that barbiturates have a vasodilatory effect within several vascular

regions would more nearly point to a change in the muscular tone of the vessels insignificant in regard to the functional activity.

Finally it should be pointed out that the demonstrated changes of the relative specific activities may be due to an increase of vascular permeability. Marx (1931) has assumed that such is brought about by barbiturate because of the fluid retention within the organism during narcosis with barbiturates. The cerebral oedema which often develops in barbiturate poisoning might also be interpreted in the same manner (Tatum). An increase of permeability which may be caused by vaso-dilatation (cf above) need not mean any functional change *in loco*. There is the possibility that the relative high concentration of barbiturates within the brain stem, reported by Pick and Keeser & Keeser, compared with other parts of the brain, may be due to such an increase of permeability whose effect should be more obvious within the highly vascular hypothalamus than elsewhere.

4. Experimental sleep research.

The results of the experimental sleep research with animals have been discussed in Chapter II. These results played an important rôle in the discussion which led to the interpretation that the hypothalamic centre for sleep regulation is a sleep centre. Furthermore this discussion, involving the seemingly paradoxical circumstance that stimulation as well as tissue destruction within the region of the sleep centre induces sleep, resulted in the interpretation that the sleep effect of electrolytic lesions is of humoral character and that sleep-inducing substances are liberated from the necroses. The postulated substances should not be non-specific products of the necroses but physiological substances specific for the posterior part of the hypothalamus of animals with monophasic diurnal sleep rhythm. Such an assumption however anticipates that the specific sleep-inducing activity of the substances is not incapacitated when the necroses are formed. As earlier pointed out (p. 30), the tissue injury is the result of electrolysis and not of thermocoagulation, and therefore the assumption of preservation of a specific activity in respect of the postulated substances would seem justifiable.

The assumption that the postulated sleep-inducing substances are a physiological phenomenon leads to the conclusion that they must be

formed within the hypothalamus. (An accumulation of the substances in ready-made condition is of course theoretically presumable, but, maybe, scarcely probable.) Then the question arises as to whether there is any support for the assumption that cells within this part of the brain are capable of secretory activity. This mode of function seems on the whole to be foreign to the central nervous system. In the following chapter however attention will be drawn to some histological details and experimental results which are interpreted as support for the existence of secretory activity of nerve cells.

CHAPTER IV.

The question of neurosecretion within the hypothalamic centres.

1. Histological signs of neurosecretion.

Although of recent years the hypothalamus has occupied an increasingly prominent part in the discussions respecting a number of the vital functions of the organism, comparatively little interest has been devoted to the histological structure of this part of the brain. In the recent literature the occurence of colloid formation within the nerve cells adjacent to the third ventricle is only referred to *en passant*. The chief credit is due to SCHARRER for having investigated this part of the histology of the hypothalamus. In a number of works he has described intracellular colloid within the nerve cells of the *nucleus supraopticus* and *nucleus paraventricularis* of amphibia, fish, reptiles and mammals. He has also, like his collaborator GAUPP (1933) and DIVRY (1934), ROUSSY & MOSINGER (1934) and PETERS (1935), demonstrated colloid within the above mentioned cell groups in man. In a larger paper (SCHARRER & SCHARRER 1940) the experience in this field of research has been collected and discussed. The authors appear to be convinced that, here, one is dealing with signs of active secretion from the nerve cells, in fact, with real *neurosecretion*. As distinct from this view COLLIN (1928) is of the opinion that the colloid within the nerve cells consists of the hormones of the posterior lobe of the hypophysis, which have been transported via the perivascular lymph spaces and along the nerve fibres to be finally lodged in the nerve cells of the hypothalamus. CUSHING (1933) shares COLLIN's view. SCHARRER (1933) maintains, on the other hand, that even if COLLIN's view might hold in respect to the parts of

the brain adjacent to the hypophysis, such an accumulation of colloid within cells further away, would almost be out of the question. All the authors apparently agree that the colloid of the nerve cells is a physiological phenomenon.

The colloid described by Scharrer and others has the appearance of round granules, varying in size and in the number within each cell (Fig. 15). In one cell there may be a number of smaller granules while a neighbouring cell contains one or maybe a few large ones. Stained with Htx van Gieson these granules take on a red colour, but with defective differentiation of Htx they become grey or greyish blue. They stain red also in Htx eosin, and appear, when stained by other methods, too.

The present author has observed intracellular colloid granules of a different type within two other cell groups within the juxtaventricular grey matter. Their staining properties were also quite different. To begin with the "Tuchechtgelb" stain of Wallart & Houette (1934) was employed, but later the acid violet stain of Gellerstedt[1] (not published) was used for a long time. Both these methods were given up however, the former due to its unreliability, the latter because it was so time-consuming. Latterly a modification of the azan stain, here called AL stain[2], has been used. (The granulations show up with the azan stain also, but the dark contrast colour and the poor differentiation render the granules difficult of observation.)

The colloid substance stains a bright red with this AL method, and thus stands out conspicuously against the green or bluish green contrast colour. The structure of the tissue is also shown up quite satisfactorily.

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[1] *Acid violet stain* according to Gellerstedt (fixation in formalin, paraffin, 5 μ sections): 1) Acid violet (0.25 % in 25 % alcohol with 0.5 % carbolic acid) heated above flame. 2) Differentiation in 40 % alcohol. 3) 3 % water solution of "tuchechtgelb" (Ciba) 1—2 min. 4) Safranine (0.25 % in 1 % carbolic acid) some mins. 5) Differentiation in 2 % formolic acid. 6) 99 % alcohol—xylol, mounted in balsam.

[2] *AL stain* (fixation in formalin, paraffin, 5 μ sections). 1) 0.5 % azocarmine in 1 % HAc, 1 hour. 2) Aq. dest. 3) Differentiation in aniline oil-alcohol (1 % aniline oil in 90 % alcohol). 4) 95 % alcohol with 1 % HAc. 5) 5.5 % water solution of phosphowolframic acid, 1—3 min. 6) Aq. dest. 7) 0.5 % light green water solution, some min. 8) 95—99 % alcohol—xylol, mounted in balsam.

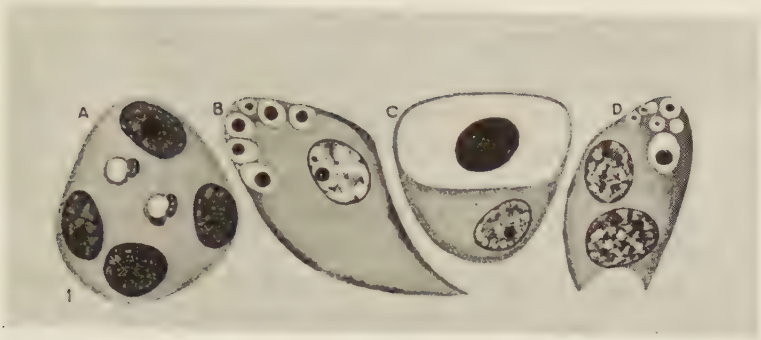


Fig. 15. Intracellular nerve cell colloid from human *nucleus supraopticus* and *nucleus paraventricularis* (from Scharrer & Scharrer 1940 and Scharrer & Gaupp 1933).

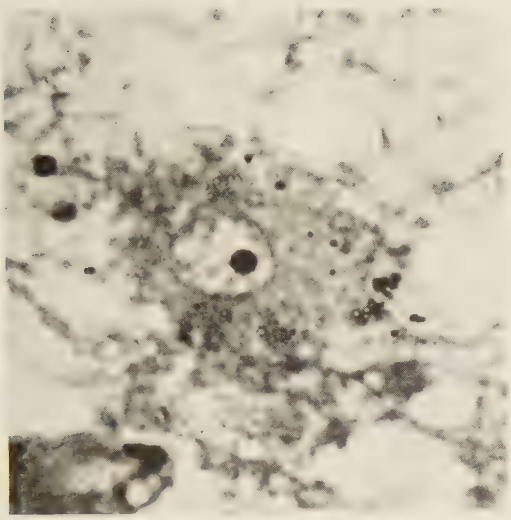
It has not been possible to find any colloid within the nuclei supraopticus and paraventricularis of human beings, with these three staining methods. On the other hand, colloid has been found to occur in some cell groups situated in the central part of the brain stem, namely, the *nucleus tuberomamillaris* (s. *mamillo-infundibularis*) and *nucleus raphes*[1] in the mesencephalon and anterior pontine region. These two cell groups form the only sites within the central nervous system of human beings in which colloid has been detected with these staining methods.

With reference to the colloid staining it should also be pointed out that it is impossible to detect the colloid with Htx van Gieson and Htx eosin stain. It has no colour of its own either. It cannot be demonstrated by using fat stains. The fact that it is stained by the Spielmeyer myelin sheath stain, as GELLERSTEDT (1933) has pointed out with reference to nucleus raphes, may indicate that the colloid is, or contains a substance akin to the lipo-proteins.

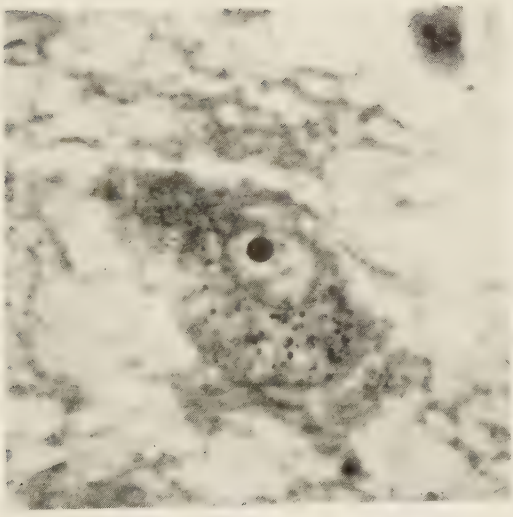
Unlike the earlier observed colloid in nuclei supraopticus and paraventricularis, with its great variation in size of the grain, the granules in nuclei tuberomamillaris and raphes are very uniform in size. A single granule usually measures 1 μ in diameter. The number of granules in each cell varies considerably. In one cell there may be many granules and the next may be quite free from colloid. The position of the granules also varies from cell to cell. They generally lie together in some part of the cell body, but are often scattered or lie in a few small groups.

Like the majority of other cell groups within the juxtaventricular grey matter of the brain stem, nuclei tuberomamillaris and raphes are not well demarcated histologically. With reference to the expansion of the groups outside their main localization, there are considerable individual variations. One often finds cells typical of nucleus tuberomamillaris, including colloid, right up to the region of nucleus paraventricularis. They also appear in the form of a

[1] The nomenclature of the cell groups in the medio-ventral part of the grey matter around the aqueduct is very confused. Scarcely two handbooks coincide as to the naming of the various groups and the lines of demarcation between them are dissimilar. Here, and in the following, *nucleus raphes* indicates those cell groups which in Ranson's "Anatomy of the nervous system" are called nucleus raphes dorsalis, nuclei tegmenti and nucleus centralis superior.



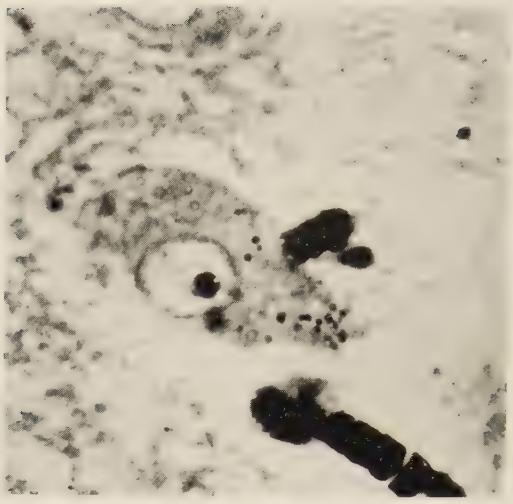
a



b

Fig. 16 a—b (microphotographs, high power magnification, acid violet stain according to Gellerstedt). Nerve cell colloid from nucleus tuberomamillaris with the dark stained colloid granules.

c



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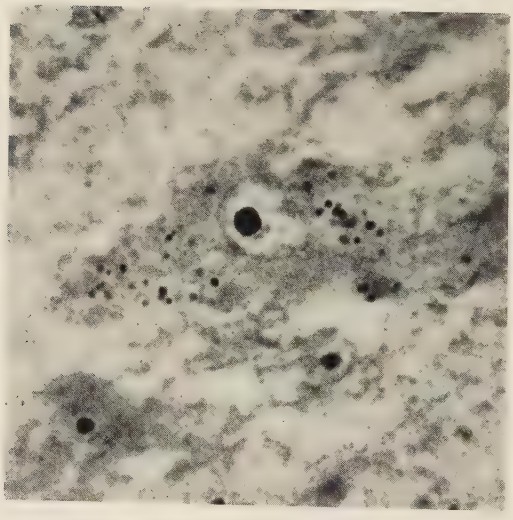

Fig. 16 c—d (microphotographs, high power magnification, acid violet stain according to Gellerstedt). Nerve cell colloid from nucleus raphes with dark stained colloid granules.

mantle round the lower part of the crus fornicis and, moreover, outlying groups of such cells are found latero-caudally in the direction of the region of substantia nigra on the dorso-medial side of the internal capsule, as well as caudally within the central grey matter of the mesencephalon. Within what is here called nucleus raphes there are, broadly speaking, two types of nerve cells, a medium sized form resembling the small cells of the nucleus oculomotorius, and a larger form, whose appearance is very similar to that of the cells within the nucleus tuberomamillaris. It is within this latter type that colloid granules can be observed. These cells lie collected near the median plane. Outlying cells of this type are regularly seen in the central grey matter towards the region of the locus coeruleus, and also laterally on the dorsal side of the transversal pontine fibres.

By reason of the histological similarities between these two colloid-containing cell groups and owing to their similar situation in relation to the ventricular system, it would not seen out of place to assume the existence of a connection in some form or other between them. An anatomical connection has been shown to exist by means of serial sections. Fig. 17 shows a series of diagrams of transverse sections of the brain stem showing the colloid-containing system, nuclei tuberomamillaris and nucleus raphes. The series also shows the system of pigment-containing cells within these regions, substantia nigra and locus coeruleus. This is because the colloid- and the pigment-containing cells are mixed together within the boundary regions between the nucleus tuberomamillaris and substantia nigra as well as between the nucleus raphes and locus coeruleus. Occasionally cells containing both colloid and pigment are to be seen in these boundary regions. These scattered pigment-containing cells are moreover frequently found in an unbroken chain between the substantia nigra and locus coeruleus. Thus the above statements might perhaps justify the conception of these four cell groups (nuclei tuberomamillaris and raphes, substantia nigra and locus coeruleus) as an anatomical unit, which in turn, may indicate some functional connection. Unfortunately such an assumption throws no light upon the possible physiological significance of the colloid, as nothing is known with certainty about the function of the pigment-containing cell groups. The brown pigment within the locus coeruleus begins to

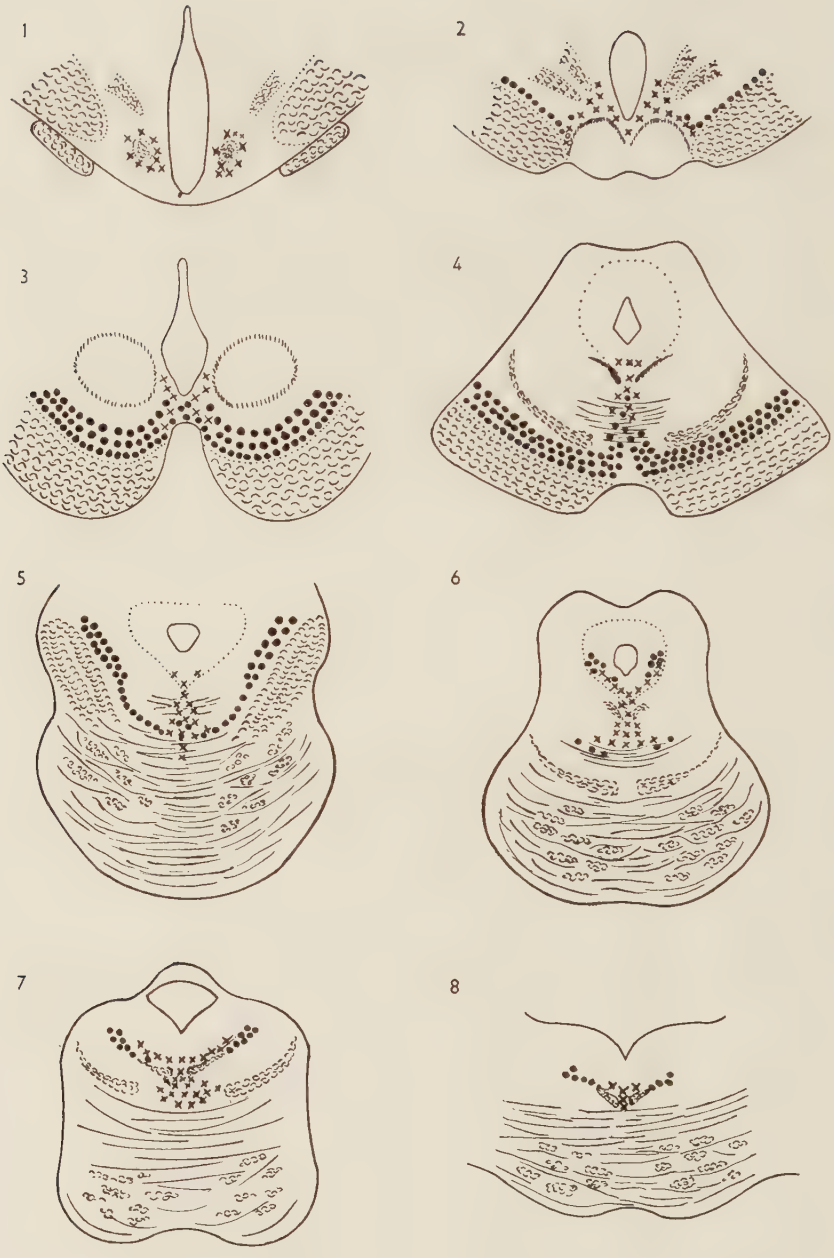

Fig. 17. A series of schematic diagrams of transverse sections of the brain stem showing the colloid-containing cells of the nuclei tuberomamillaris and raphes, marked with ×, and the pigmented cells of substantia nigra and locus coeruleus, marked with •.

develop about the same time of life as the colloid (see below), but that of the substantia nigra begins some years later (cf Spatz 1935). The pigment is formed as such. As far as can be seen from the author's own material, it has no precursor with staining properties like those of the colloid. This indicates that pigment and colloid are two distinct substances.

The investigated material consists of more than 300 brains selected at random from a year's collection of about 500 autopsies here at the Institution. Owing to the nature of the material the higher age groups predominate. Moreover, cases with different endocrine disturbances and psychosis have also been investigated.

Colloid granules were found within nucleus tuberomamillaris and nucleus raphes in every case above the age of 2 years and were absent in every case below 1 year. It was not possible to define accurately the age at which the colloid first appeared because the material within these age groups was so small. No correlation was found between the quantity of colloid and any disease or symptom of disease, and this agrees with the statement concerning the colloid within nuclei supraopticus and paraventricularis (Gaupp, Peters). The previously mentioned unequal distribution of colloid within the nuclei tuberomamillaris and raphes means that great caution must be shown however in determining the amount of colloid, and it causes the estimation to be particularly subjective. For this reason the author has desisted from the attempt to obtain any more exact measure of the colloid in the individual case. Widely seen, it can be said however, that no significant variations of the quantity of colloid have been observed in this investigated material. Even in the very aged, colloid was found to be present in about the usual quantity. As regulation centres for a number of vegetative-endocrine functions are located within the hypothalamic region, which display a monophasic diurnal rhythm, the time of day when death occurred was noted when estimating the colloid quantity. But no differences were observed in this respect either. The various kinds of medication were not found to bring about any palpable changes in the amount of colloid.

The fact that colloid within nuclei tuberomamillaris and raphes is a constant phenomenon during the greater part of life, argues with certainty that it cannot possibly be a pathological change in the cells. When attempting to form an opinion of its origin it

would not seem out of the way to accept the view of SCHARRER and others that colloid, as such, is formed by the nerve cells themselves, and that it is not an accumulation of hypophysial colloid. Of course it is conceivable that hypophysial hormones in solution could be transported through the brain tissue up to the pons region. But it seems highly improbable that colloid granules should be transported through the hypothalamic tissue in the manner assumed first by HERRING (1908) and later by COLLIN and CUSHING. The said authors regard the hypophysis as a partially holocrine gland and the colloid granules as parts of dead hypophysial cells. Moreover, when these colloid granules assume a size sometimes exceeding that of a red blood corpuscle, it would seem incredible that such particles could pass through the minute tissue spaces and directly through the tissue of the brain. If, in reality, the colloid granules lying free in the hypothalamic tissue are parts of dead nerve cells in part transformed into colloid, as many of SCHARRER's figures seem to indicate, such a condition can be taken as evidence that within this part of the brain, cells are dying continously. Such a degeneration of the nerve cells throughout the life must in some way be replaced by formation of new cells, which may perhaps be indicated by the existence of bi- and multinucleated nerve cells.

Thus, although there is reason to assume that nerve cell colloid is a physiological phenomenon, it is more problematic as to whether it is to be regarded as a substance, secreted by the cells, which has endocrine or similar activity. In this respect our knowledge is incomplete. For instance, it is not known whether colloid granules in the cells of the anterior lobe of the hypophysis are identical with the endocrine secretions of this gland. It may seem improbable that all the hormones, soon amounting to twenty, which have been isolated from the hypophysis, will be represented by the two types of granule. Against this can be pointed out however that histotechnique is too imperfect at present to allow of distinction between a large number of types of granules.

When it is maintained that the histological pictures within certain groups in the hypothalamus and adjacent centres indicate secretory activity, one may, as SCHARRER and GAUPP have pointed out, not only obtain support from the occurrence of colloid granulation, but also take into account the general structure of the tissue, involving particularly the abundance of capillaries and the intimate relation

between the nerve cells and vessels. The vascularity of the periventricular grey matter of the brain stem is remarkably great. This circumstance has especially been pointed out in respect to nuclei supraopticus and paraventricularis (cf FINLEY 1940) but it holds good even though to a lesser extent for other parts of the vegetative centres within the hypothalamus and adjacent parts of the brain stem. The intimate relation between vessel and nerve cell is characteristic of the nuclei supraopticus and paraventricularis (HECHST 1930 and others) as well as of nuclei tuberomamillaris and raphes, a fact evident in the present material. Moreover, intracellular capillaries have been described (SCHARRER), but such have not been observed in the present material. Another histological characteristic of these regions is the occurrence of bi- and even multinucleated nerve cells. Such cells have been observed within nuclei supraopticus and paraventricularis (HECHST, SCHARRER). In the present material cells with two nuclei occurred in nuclei tuberomamillaris and raphes off and on, while multinucleated cells were not observed. It should also be pointed out that nerve cells with two or more nuclei are an extreme rarity within other parts of the brain.

The occurrence of colloid granules is *per se* no conclusive proof of secretory activity, any more than a negative finding in this respect proves the absence of such a function in an organ. Maybe the strongest support for a presumptive neurosecretion in the hypothalamic centres is the fact that the neurohypophysis, an admittedly endocrine organ, is to be regarded as part of the hypothalamus. As is known the posterior lobe of the hypophysis is formed as an outgrowth from the embryonic hypothalamus. When accordingly a part of the hypothalamus, i. e. the neurohypophysis, has demonstrated its capacity for endocrine activity, there would seem to be the possibility of other parts of the hypothalamus having the same type of function. At present however it cannot be said whether possible secretory activity in certain cells within the hypothalamus excludes a simultaneous nervous function of these cells.

Finally it should be pointed out that a number of animal species have been investigated with respect to the occurrence of colloid within the brain stem. The animals examined are the cat, rabbit, guinea pig, white rat, white mouse, horse, cow, pig, and hedgehog. Using the above mentioned three staining methods no colloid sub-

stance was observed within the vegetative centres in the brain stem of these anmials. Attention has already been drawn however to Scharrer's earlier comparative anatomical investigations in which he demonstrated the occurrence of colloid in a number of widely differing animal species including some of the above named. The negative find need not indicate that the hypothalamic centres of these animals function in a manner different from the corresponding parts of the human brain. The colloid stainability is obviously variable from cell group to cell group and from animal species to animal species. Furthermore, as previously stated, the occurrence of colloid is not a necessary condition for the presumption of a secretory function in cells, whether located in the central nervous system or anywhere else in the organism.

2. Experimental proofs of neurosecretion.

It is of considerable interest that one finds in the literature a number of reports which show that the hypothalamus tissue really contains substances having endocrine activity. An essential part of these investigations has proceeded from the assumption that the secretory products of the hypophysis should have one of their seats of action in the hypothalamic centres, and that they should be transported there via the stalk of the hypophysis (e. g. Abel 1924, Collin & Drouet 1933). It has also been proved in a decisive manner (Borell 1945) that the thyrotropic hormone which can be demonstrated in the tuber cinereum originates from the hypophysis as no such hormone is to be found within part of the brain in question after hypophysectomy.

Transport of endocrine substances from the hypophysis to the hypothalamus must be assumed to take place direct through the brain tissue (cf Cushing p. 47), because there are no certain direct communication with blood vessels between the two locations in question. Popa & Fielding (1930), it is true, have published observations of a portal circulation between the hypophysis and the hypothalamus. Later authors (Wislocki & King 1936, Finley 1940) however, have not been able to verify these observations.

Yagi (1936) has demonstrated that saline extract from the hypothalamus of rabbits are capable of raising the blood sugar when

injected into animals of the same kind. Extract from other parts of the brain proved not to have this effect. YAGI makes no statement however as to where the substances responsible for this effect are formed.

However, among these investigations there are some which are of particularly great interest in this connection. TRENDELENBURG (1928) and SATO (1928) have both demonstrated that the amount of anti-diuretic and oxytocic substances within the tuber cinereum after hypophysectomy does not decrease but, on the contrary, there occurs a definite increase. These two authors interpret their results as meaning, that the formation of the said hormones, which occurs under normal conditions, is intensified after hypophysectomy as a compensatory reaction.

Similar observations, in principle, have been made by WEISSCHEDEL & SPATZ (1942) regarding the gonadotropic hormone. These authors implanted tuber cinereum tissue subcutaneously in immature female rats which then manifested a premature ovarian maturity. This reaction was also obtained after the injection of saline extract from the tuber cinereum. The same result was achieved even if the animals from which the tuber tissue had been taken, had undergone hypophysectomy earlier. The said authors therefore consider that not only the hypophysis but also the tuber cinereum has the capacity to form gonadotropic hormones.

These experimental results must be looked upon as proof that cells within the hypothalamus, that is to say, within the brain itself, are capable of producing substances which have the same effect as hormones.

3. Neurosecretion and sleep function.

In accordance with what has already been considered as probable (Chapter II and III) the centre for sleep regulation within the posterior part of the hypothalamus and adjacent part of the central grey matter of the mesencephalon, is to be regarded as a *sleep centre,* that is to say, a centre whose increased activity induces sleep. Earlier discussions have led to the interpretation that the sleep effect of electrolytic lesions within the region of this sleep centre is the result of a *humoral* mechanism. The sub-

stances supposedly responsible for the sleep effect would, in such a case, be specific for the parts of the brain stem in question of animals with monophasic diurnal rhythm for sleep-wakefulness. Attention is drawn in the present chapter to histological as well as experimental support for the presumption of a *secretory function* in the hypothalamic and neighbouring centres.

If now these facts and results of the discussions be connected, one asks whether the postulated, sleep-inducing substances from electrolytic lesions might not be physiological secretory products regulating sleep derived from cells within the region of the sleep centre. This way of thinking results in a new *working hypothesis* for further sleep research, which can be formulated thus: Sleep is a neurosecretorily regulated, hypothalamic function; through the secretion of sleep-inducing substances, the sleep-intermediatory effector organs of the hypothalamus are affected in such a manner that sleep ensues.

The verification of such a "neurocrine" theory of sleep would obviously depend on the extraction of sleep-inducing substances from the hypothalamic tissue. Some tests of this type have been performed in connection with this investigation, but they have not led to any positive results. Thus, saline extract from the hypothalamus of rabbits injected intravenously in rabbits has not produced any demonstrable sleep effect. It must be mentioned however that this result was not unexpected with reference to the earlier presumption that the polyphasic animal lacks a proper sleep function. Extract from the hypothalamus of the cow injected intraperitoneally in cats did not induce any noticeable sleep effect either. It is not absolutely certain however whether the cow is to be reckoned as a polyphasic or monophasic animal.

In the previous extract tests (cf p. 76) no sleep effect was recorded. Obviously this was not to be expected as the region of the sleep centre is situated immediately behind the tuber tract. Sato also tested extract from the corpora mamillaria with respect to anti-diuretic effect, but these experiments were made with rabbits. Furthermore it may be difficult to observe any tendency to sleep effect which may occur, especially when one is not prepared for such an effect. Sleep is furthermore so easily prevented by various kinds of factors which are not easy to control in animal tests.

It should also be pointed out that the above working hypothesis

is not to be considered as indicating any particular one of the hypothalamic cell groups referred to in this chapter as being responsible for sleep regulation. It can only be pointed out that injuries within these regions are frequently combined with sleep disturbances. It would not seem out of place to mention in connection with the above hypothesis that the colloid within the nucleus tuberomamillaris and nucleus raphes begins to develop at about the same time of life as the monophasic sleep rhythm develops from the earlier polyphasic rhythm.

If the assumption of a humoral = neurocrine sleep regulation be correct, what is it then that induces the diurnal rhythm in the activity of the sleep centre? The primary causes are obscure, but this is also true of all the other diurnally rhythmic functions within the organism. No diurnal rhythmic variations in the amount of colloid were demonstrated within the hypothalamic region. But, as earlier pointed out (p. 74) it seems improbable that the colloid and the postulated secretory products should be identical. No reports have been given, as far as the author knows, concerning any diurnal rhythmic changes in the histology of the organs which have definitely demonstrated endocrine functions, although many of these glands are concerned in the regulation of functions having a diurnal rhythm. As earlier mentioned, the sleep, and accordingly the postulated neurosecretion regulating the sleep, is easily influenced by various chemic-toxic, endocrine, sensory and psychic factors (p. 54). In many respects sleep may be regarded as the result of a conditioned reflex in Pavlov's sense. These circumstances evidently do not argue against the hypothesis of a neurocrine sleep regulation. With regard to the supposed secretion itself there are two possibilities concerning the rhythm. It is either a question of a rhythmic production or it is a rhythmic secretion of continously produced substances. In this respect, our knowledge of the activity of the endocrine organs is particularly deficient.

How does a "neurocrine" hypothesis stand in regard to our knowledge of the various details of the sleep function? It can, on the whole, be said that no known condition within the physiology and pathology of sleep argues against such a theory. With respect to the results of the sleep research on animals from which the theory is mainly derived, it is found that the hypothesis is capable of giving a unitary interpretation to all the fundamental results, which is

not the case regarding earlier theories that have generally been clearly contradicted by one or more experimental observations. But it should once more be called to mind that the theory is at present nothing more than a working hypothesis which will indicate a new direction of approach for further investigations on the physiology of sleep.

SUMMARY.

The literature on the physiology and pathology of sleep infers that a regulation centre for sleep-wakefulness must exist within the posterior part of the hypothalamus. It is not yet elucidated however as to how this centre functions. HESS' experiments which revealed that *stimulation* of this part of the brain of cats induces sleep, have been accepted as proof that the centre is a *sleep centre,* that is to say, that the centre produces sleep by reason of the enhancement of its activity. RANSON's tests which displayed evidence that *tissue destruction* within the same region of the brain of cats and monkeys also induces sleep has, on the other hand, indicated that it is a question of a *wakefulness centre,* namely, that the adequate activity of this centre is requisite for the preservation of the state of wakefulness. These two theories are in direct opposition to each other.

The author has worked out an *X-ray stereotaxic method* in order to render subcortical parts of the brain available to localized, experimental intervention. In an investigation with *electrolytic lesions within the posterior part of the hypothalamus of cats,* RANSON's results were reproduced. The effect of the intervention is a sleep period of some days duration. The employment of nitrous oxide anesthesia, out of which the animal can be wakened after some few minutes, has elucidated however that *this sleep period does not set in immediately after the operation, but after an interval of some hours.* This circumstance which has not been pointed out earlier, would seem to complicate the problem still further.

A theoretic possibility of giving a unitary interpretation of the results of both HESS and RANSON appears to the author as follows. The sleep regulation centre within the posterior part of the hypothalamus should be apprehended, in conformity to the assumption of HESS, as a *sleep centre.* The sleep effect induced by the destruc-

tion of tissue within this region should presumably be brought about by substances which are liberated from the necroses, transported to and affecting the surrounding parts of the brain (such as other, adjacent vegetative centres, the thalamus and the extrapyramidal centres of the brain stem) which, as regards the sleep function, are under influence of the hypothalamus. The said substances must be apprehended as affecting these sleep-intermediatory brain centres in the same way as the influences issuing from the hypothalamus which physiologically induce sleep. By reason of the fact that no similar tissue injury within other parts of the brain exterior to the boundaries of the posterior part of the hypothalamus produce sleep, the conclusion might be drawn that the postulated sleep-inducing substances are not non-specific products of the necroses but occur preformed in this part of the brain, and that accordingly, they constitute a specificum for the posterior hypothalamic region.

Such a *humoral* mechanism for the sleep effect of hypothalamic electrolytic lesions moreover affords a plausible explanation of *the three-phase course* (wakefulness—sleep—wakefulness) after this intervention. It must be presumed of course that a certain amount of time, corresponding to the sleep-free interval, is required before the concentration of the sleep-inducing substances within the sleep-intermediatory centres have reached a sufficiently high level for sleep effect. The awakening after the sleep period, in its turn, would be due to the necroses being exhausted of these postulated, specific substances.

It has been demonstrated in this work that *electrolytic lesions within the posterior part of the hypothalamus of rabbits bring about no sleep effect.* This circumstance renders the presumption possible that the rabbit lacks sleep function and consequently also a regulation centre for sleep. The many and short periods of inactivity in animals with polyphasic diurnal rhythm of activity would accordingly not be the result of the function of a hypothalamic sleep centre, and not sleep in the same meaning as that of human being and animals with monophasic sleep rhythm.

The condition of the experimental animal with respect to the regulation of sleep after the termination of the acute sleep effect of electrolytic lesions is not yet satisfactorily elucidated. Chronic states of sleep have never been described in the literature or been observed by the author. Probably the experimental animals employed

in the present investigation have been more active after the sleep period than is normal, which may possibly indicate hyposomnia.

A parallel can be drawn between encephalitis lethargica and the effect of hypothalamic electrolytic lesions. The most plausible interpretation of the sleep disturbances incidental to the stages of this disease are assumably [acute inflammation—stimulation—sleep] and [chronic inflammation with disappearance of nerve cells—diminished function—hyposomnia]. The conditions relative to the late after-course following electrolytic lesions and in respect of encephalitis lethargica argues furthermore in favour of the presumption that the centre is a sleep centre and not a wakefulness centre.

The sleep effect of the barbiturates is discussed. As a divergence from the almost generally accepted opinion that these drugs have a depressant effect on the functions of the central nervous system, the possibility is expressed that the barbiturates in *hypnotic* dosage could act in a *stimulating* manner, either directly or indirectly, on the hypothalamic sleep centre. This assumption has been deduced from the facts that the barbiturates are more or less inactive in postencephalitic states, and that sometimes a paradoxical effect of these drugs is to be seen. The author has performed some experiments to ascertain the extent of the accumulation of radio-active phosphate (containing the radio-active phosphorus isotope ^{32}P) within different parts of the brain, under the influence of small doses of barbiturate, as compared with normal conditions. It was proved that the difference between the accumulation of ^{32}P within the hypothalamus on the one hand and thalamus (in cats and rabbits) and nucleus caudatus (in cats) on the other increased under the influence of barbiturate. These results allow of no definite conclusions, but neither do they argue directly against the above mentioned possibility of a stimulating effect of the barbiturates on the hypothalamus.

Certain histological characteristics in respect to the hypothalamic region have been studied. Reports have been published in the literature concerning colloid formation within the nerve cells of nuclei supraopticus and paraventricularis, and attention has also been called to the considerable abundance of vessels within this region as well as to the intimate relation between nerve cells and capillaries and furthermore to the existence of binucleated and polynucleated cells. This has led to the conclusion that this part

of the brain is capable of *neurosecretory* function (Scharrer; Gaupp; Divry; Roussy & Mosinger; Peters; and others). Some experimental investigations in the literature have strongly supported such an assumption, in that both antidiuretic, oxytocic and gonadotropic substances have been found within the hypothalamus, which substances must have been formed within this part of the brain (Trendelenburg; Sato; Weisschedel & Spatz).

Similar histological characteristics (*i. e.* colloid granulation, abundance of vessels, intimate relation between nerve cells and capillaries, binucleated cells) have been demonstrated by the author within the human *nucleus tuberomamillaris* and *nucleus raphes* in the mesencephalon. Between these two cell groups and furthermore between them and the pigment-conveying cell groups *substantia nigra* and *locus coeruleus,* anatomical connections have been demonstrated. The formation of the colloid granulation observed within the nuclei tuberomamillaris and raphes begins during the second year of human life. These histologic characteristics are interpreted as a sign of *neurosecretion,* that is to say, of secretory activity of nerve cells, within the hypothalamic centres. This coincides with the opinions of the above mentioned authors.

The author connects the presumption of neurosecretion in the hypothalamic region with the results which indicate that the sleep effect of hypothalamic electrolytic lesions is brought about by the liberation of physiological substances, specific for this part of the brain. These two interpretations of earlier and the present experimental results together form the basis of a *working hypothesis* for continued investigations on the sleep problem, namely, that sleep should be a hypothalamic function of neurosecretory nature, and that the substances secreted from such a centre should influence the sleep-intermediatory effector organs of the hypothalamus in such a manner that sleep ensues. The question as to the cause of the monophasic diurnal rhythm must be left open. Such a "neurocrine" theory of sleep affords the possibility of uniformly interpreting the observations from animal experimental sleep research and would not seem out of accordance with the essential facts respecting the physiology and pathology of sleep.

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